A STUDY ON ASSOCIATION OF SUBCLINICAL HYPOTHYROIDISM WITH ACUTE ISCHEMIC STROKE

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In partial fulfillment of regulations
For award of the degree of
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BONAFIDE CERTIFICATE

This is to certify that dissertation named **"A STUDY ON ASSOCIATION OF SUBCLINICAL HYPOTHYROIDISM WITH ACUTE ISCHEMIC STROKE"** is a bonafide work performed by **Dr. M. Saranya,** post graduate student, Department of Internal Medicine, Kilpauk Medical College, Chennai-10, under my guidance and supervision in fulfillment of regulations of the Tamilnadu , Dr. M.G.R Medical University for the award of M.D. Degree Branch I (General Medicine) during the academic period from May 2012 to April 2015.

Prof. Dr.R.Sabaratnavel M.D.,
Professor and Head
Department of Medicine
Kilpauk Medical College,
Chennai- 10

Prof. Dr.Mayilvahanan M.D.,
Professor and Unit Chief
Department of Medicine
Government Royapettah Hospital
Chennai-14

Prof. Dr. N. Gunasekaran M.D., DTCD.,
The DEAN
Government Kilpauk Medical College,
Chennai - 600 010

DECLARATION

I solemnly declare that this dissertation **"A STUDY ON ASSOCIATION OF SUBCLINICAL HYPOTHYROIDISM WITH ACUTE ISCHEMIC STROKE"** was prepared by me at Government Kilpauk Medical College and Hospital, Chennai, under the guidance and supervision of **Dr. R.Sabaratnavel M.D.**, Professor, Department of Internal Medicine, Government Royapettah Hospital, Chennai.

This dissertation is submitted to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai** in partial fulfillment of the University regulations for the award of the degree of **M.D. Branch I (General Medicine)**.

Place: Chennai

Date: **(Dr. M.SARANYA)**

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CONTENTS

ABSTRACT

BACKGROUND

Stroke is one of the leading causes of morbidity and mortality in the general population. Apart from conventional risk factors, identifying potential modifiable risk factors can play a significant role in stroke prevention and outcome.

AIMS AND OBJECTIVES

This study aims to determine the frequency of subclinical hypothyroidism in patients presenting with acute ischemic stroke, its association with altered lipid metabolism and its role as an independent, modifiable risk factor in stroke prevention.

MATERIALS AND METHODS

85 patients presenting with acute ischemic stroke are taken as cases and 85 patients without stroke as controls matched for age,sex and risk factors. CT brain is done to confirm the diagnosis and thyroid profile measured.

Patients with normal free T3, T4 and serum TSH above upper limit of normal are diagnosed to have subclinical hypothyroidism.

The presence of subclinical hypothyroidism in both the cases and controls and its association with lipid abnormalities are analysed.

OBSERVATION AND RESULTS

Among the 85 patients with acute ischemic stroke, data analysis showed that 8.23% (7 out of 85) of them had subclinical hypothyroidism which was statistically significant with a p value of 0.007. Subjects in the control group had no subclinical hypothyroidism. Among the 7 cases with subclinical hypothyroidism, 6 (85.7 %) of them had positive correlation with serum total cholesterol which was statistically significant.

CONCLUSION

The study results show a significant association of subclinical hypothyroidism with acute ischemic stroke and signifies its potential role as an independent, modifiable risk factor in stroke prevention.

INTRODUCTION

Stroke or cerebrovascular accident is defined as an abrupt onset of a neurological deficit, either focal or global that is attributable to a vascular etiology. Definition of stroke is thus clinical and laboratory studies including brain imaging are used to support the diagnosis.

The term cerebrovascular disease defines any brain lesion resulting from a pathologic process of the blood vessels such as occlusion of the lumen by embolus or thrombus, rupture of a vessel, an altered permeability of the vessel wall or a change in the quality of the blood flowing through the cerebral vessels. These are two main types—ischemia, with or without infarction and hemorrhage.

There are two main types—ischemia, with or without infarction and hemorrhage. Stroke can also be classified in terms of the underlying pathogenesis involved, i.e., atherosclerosis, arteriosclerotic changes developing secondary to Hypertension, arteritis, aneurysmal dilatation and developmental vascular malformations of the brain.

The clinical manifestations of stroke are highly variable because of the complex anatomy of brain and its vasculature. With the advent of imaging technologies, identifying a lesion as ischemia, infarct or hemorrhage has been made feasible to the attending physician. These methods help us to identify salvageable tissue during an acute phase of stroke. In advanced methods of stroke management, the objective is to identify ischemic, but not infarcted

tissue. Diffusion weighted imaging methods have been proved invaluable in stroke workup.

In recent population based studies, the rate of incidence of stroke in India is found to be 119-145/100,000. The estimated adjusted prevalence rate of stroke ranges 84-262/100,000 in rural and 334-424/100,000 in urban areas.

There are several risk factors for stroke which includes hypertension, diabetes mellitus, atrial fibrillation, cigarette smoking, and dyslipidemia. Other causes like hypercoagulable states and medications like birth control pills also contribute but only in special circumstances. In addition, hypothyroidism has been studied as an independent risk factor for causing ischemic stroke by accelerating the process of atherosclerosis.[1]

Hypothyroidism is linked to altered lipid metabolism and lower levels of HDL cholesterol and higher levels of total cholesterol/HDL-C and LDL-C/HDL-C ratios and also associated with elevated homocysteine levels.

A number of clinical case reports, epidemiological studies, case -control and cohort studies have linked hypothyroidism and atherosclerosis[2].

AIMS AND OBJECTIVES

AIMS AND OBJECTIVES OF THE STUDY

1. To determine the frequency of subclinical hypothyroidism in patients presenting with acute ischemic stroke.
2. To study the association of subclinical hypothyroidism with altered lipid metabolism and its role in atherosclerosis.
3. To study the role of subclinical hypothyroidism as an, independent, modifiable risk factor in stroke prevention.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Definition of Stroke

The World Health Organization (WHO) definition of stroke is: “rapidly developing clinical signs of focal or global disturbance of cerebral function, with symptoms lasting 24 hours or longer or leading to death, with no apparent cause other than of vascular origin ”.

Types of stroke

Stroke can either be ischemic (with or without infarction) or hemorrhagic (intracerebral or subarachnoid).

Ischemic stroke

Ischemic stroke results from occlusion of the cerebral arteries by an atherosclerotic thrombus or from an emboli arising from the proximal part of the arterial system or the heart. Cardiac rhythm disturbances like atrial fribrillation which results in stasis and blood clot formation, forms an important source of embolic stroke.

This is to be differentiated from Transient Ischemic Attack (TIA) which resolves in less than 24 hours in spite of evidence of permanent brain injury on neuro imaging.

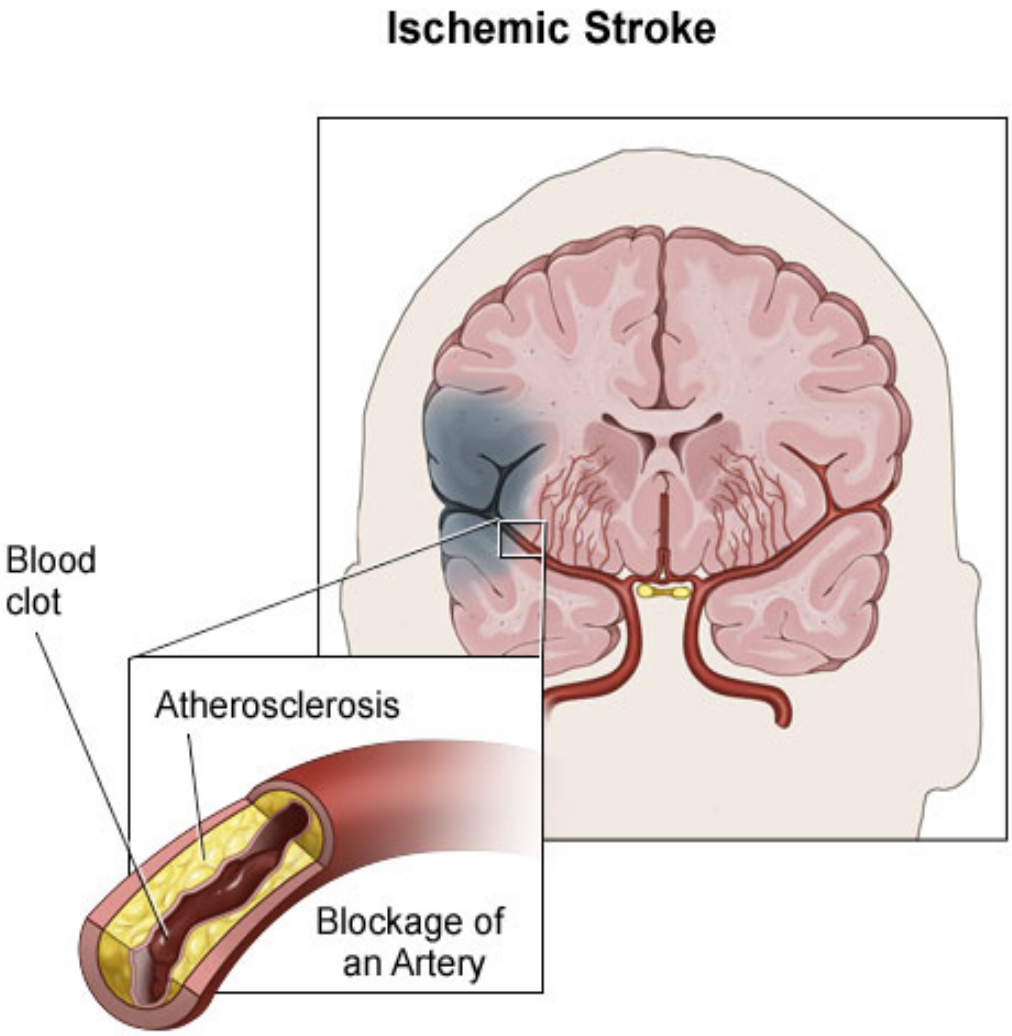

Figure 1 Atherosclerosis and acute ischemic stroke

Hemorrhagic stroke

Besides trauma as an etiology, spontaneous intracerebral hemorrhages are mainly due to arteriolar hypertensive disease, and rarely due to coagulation disorders and vascular malformation within the brain.

Intra parenchymal hemorrhage due to hypertension and subarachnoid hemorrhage due to aneurysmal rupture are the two most common causes of

hemorrhagic stroke.Hemorrhagic stroke either by its mass effect on the surrounding structures or by raising the intracranial pressure produces significant neurological deficit.

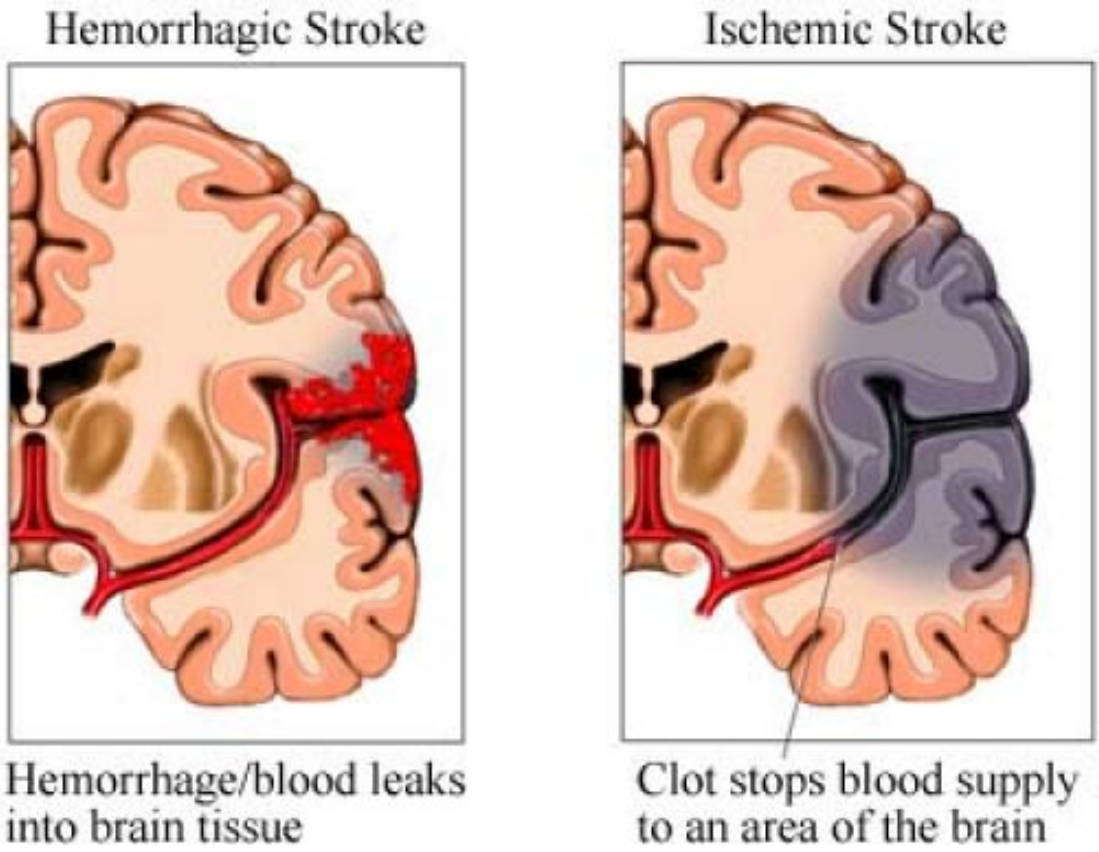

Figure 2 Types of Stroke

In intracerebral hemorrhage, blood leaks from the vessel directly into the brain and hematoma occurs which causes mass effect on the surrounding brain and physical disruption of the nerve tissue. As the leakage gets arrested, the blood slowly disintegrates and is absorbed over a period of weeks and months.

Subarachnoid hemorrhage results from rupture of aneurysms present at the branching points of the large arteries of the circle of Willis, the blood is contained within the subarachnoid spaces and therefore, causes little focal effect on the brain. However, when there is severe bleeding it causes a delayed cerebral ischemia through a mechanism of constriction of the vessels of the circle of Willis and their primary branches (vasospasm).

The Stroke Syndrome

Stroke in its mildest form may consist of a trivial and transient neurologic disorder insufficient for the patient even to seek medical attention whilst in the most severe form the patient becomes hemiplegic or even comatose.

However, the essential feature in all forms of stroke is the temporal profile of neurologic events irrespective of the grading of severity between these two extremes. The abruptness with which the neurologic deficit develops usually in a matter of seconds helps in making a diagnosis of vascular origin.

Based on Time of onset

Most embolic strokes characteristically have a sudden onset and the deficit reaches its peak almost at once. Thrombotic strokes also have an abrupt onset, but they evolve somewhat more slowly over a period of several minutes or hours and sometimes progresses in a saltatory fashion, i.e., in a series of steps. Hypertensive cerebral hemorrhage is sudden in onset but the deficit may be either static or steadily progressive over a period of minutes or hours whilst in subarachnoid hemorrhage it is almost instantaneous.

Based on pattern of involvement

The second essential feature is the focal signature of stroke. The neurologic deficit helps in localizing the anatomical site inolved and also in estimating the size of the infarct or hemorrhage. Hemiplegia stands as the classic sign of all cerebrovascular diseases, whether the lesion is restricted to the cerebral hemisphere or when it also involves the brainstem with accompanying other diverse manifestations but in highly recognizable patterns. These include paralysis, numbness and sensory deficits on one side of the body, aphasia, visual field defects, diplopia, dizziness and dysarthria. The different patterns of involvement enable the physician to localize the lesion at times so precisely to even specify the culprit artery involved.

The territory of any artery, large or small, deep or superficial, may be involved. When an infarct involves the territory of a carotid artery, unilateral signs predominate: hemiplegia, hemianesthesia, hemianopia, aphasia, and agnosias are the common manifestations. In lesions involving the basilar artery territory, the signs of infarction are frequently bilateral and occur in association with cranial nerve palsies and other segmental brainstem and cerebellar signs; quadriparesis, hemiparesis, and unilateral or bilateral sensory impairment are present coupled with diplopia, dysarthria, ataxia, and vertigo in various combinations.

Based on sequence of resolution of neurological deficit

Excluding fatal strokes another important aspect in the temporal profile of stroke evolution is the arrest and then partial regression of the neurologic deficit in almost all cases. A focal syndrome of rapid regression that reverses itself entirely and dramatically over a period of minutes or up to an hour has been defined as the "transient ischemic attack" (TIA). Often, an extensive deficit from embolism also partially reverses itself within a few hours or days. In most cases of thrombotic strokes, improvement occurs gradually over weeks and months, and there is considerable residual disability.

So a gradual downhill course over a period of several days or weeks helps in making an alternative diagnosis of non vascular etiology. However there are exceptions, as in patients with multiple vascular occlusions and progression of a focal deficit due to brain edema developing secondary to large infarctions or hemorrhage.

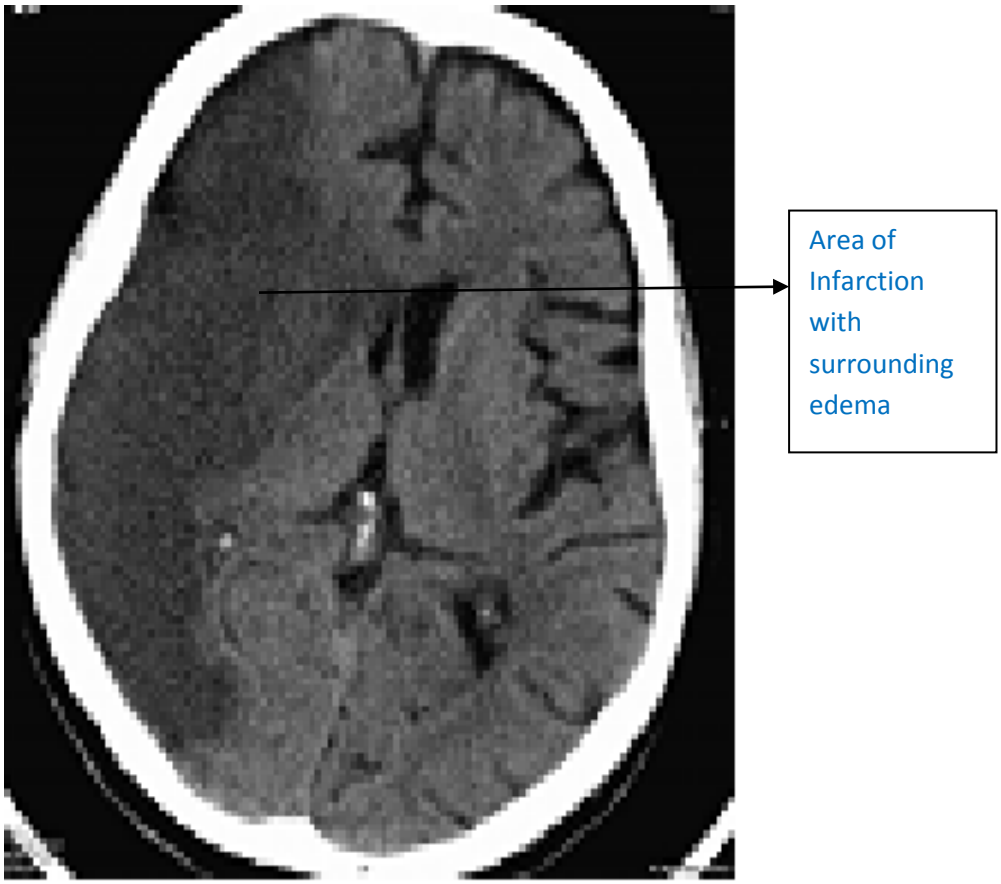

Figure 3 CT Brain Showing Infarct

Pathophysiology of Cerebral Ischemia

The brain derives its nourishment from a constant and adequate supply of oxygenated blood and this is maintained by a series of baroreceptors and vasomotor reflexes under the control of centers in the lower brainstem. So any disturbance in this hemostasis for eg the complete stoppage of blood flow for longer than 5 min produces irreversible brain damage. At autopsy, this damaged brain tissue which undergoes ischemic necrosis or infarction is seen as a zone of softening or encephalomalacia. Focal ischemic damage usually results from occlusion of an artery by a thrombus or embolus, but cardiac failure resulting in

hypotension when severe and prolonged enough, can be the cause of focal as well as diffuse ischemic changes.

Several additional ischemia-modifying factors may influence the extent of necrosis. The speed of occlusion has a significant effect- with gradual narrowing of a vessel allowing time for collateral channels to open. Hypoxia and hypercapnia have additional deleterious effects. Altered viscosity and osmolality of the blood and hyperglycemia are other important factors. Finally, vascular anomalies (of neck vessels, circle of Willis) and the presence of previous vascular occlusions also influence the outcome.

Cerebral infarcts vary greatly depending on the amount of congestion and hemorrhage found within the softened tissue. Pale infarcts are devoid of blood; few infarcts show mild congestion (dilatation of blood vessels) at their margins while hemorrhagic infarcts show an extensive extravasation of blood from many small vessels in the infarcted area.

Many infarcts show a mixed pattern. Like hemorrhagic infarction which occurs in cases of cerebral embolism, results when an embolic material, after occluding an artery results in ischemic necrosis of brain tissue, fragments and then migrates distally from its original site. This allows partial restoration of the circulation to the infarcted zone, and blood seeps through the damaged small vessels to produce hemorrhage. Stroke from occlusion of veins in the cerebrum

also show a mixed type and has special characteristics of not conforming to the territories of the main cerebral arteries and usually contains substantial hemorrhage within the infarcted zone.

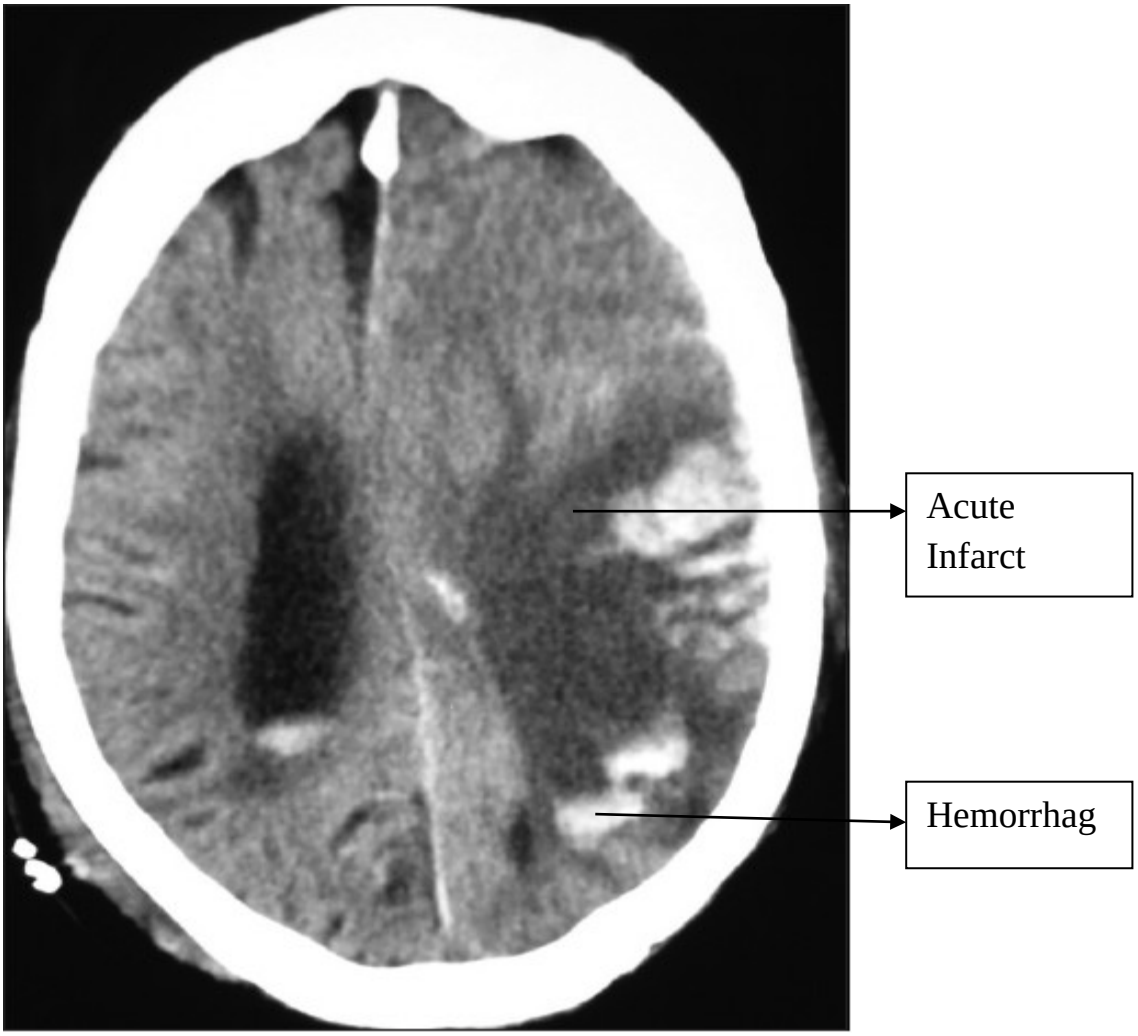

Figure 4 Infarct with hemorrhagic transformation

RISK FACTORS FOR CEREBROVASCULAR DISEASE

Important risk factors for stroke have been identified as age, sex, blood pressure, hyperglycemia, dyslipidemia, smoking, alcoholism, sedentary lifestyle and dietary habits. Besides the above mentioned factors, ischemic and valvular heart disease, atrial fibrillation and history of similar events in the past also increase the risk of stroke.

Patient's socioeconomic condition, ethnicity, educational status and environmental factors like physical (temperature, altitude), geographical, or psychosocial issues also seem to play a role.[4]

Exposure to environmental tobacco smoking have been studied as an independent risk factor for stroke. As in coronary artery disease, the level of low-density lipoprotein (LDL) cholesterol has the greatest impact on the incidence of stroke with elevated triglycerides also conferring additional risk. Other factors, such as low potassium intake and reduced serum potassium are also associated with an increased stroke rate in several studies, but the mechanism of this effect is obscure with a detrimental effect on blood pressure being a likely possibility.

HYPERTENSION AND STROKE

The longitudinal analytical study done on Framingham's[5] adult population clearly defines hypertension as a major risk factor for stroke. It is associated with an increased incidence of both haemorrhagic, ischaemic and

lacunar stroke. A transient rise in blood pressure is common in acute stroke and in cases with pre-existing chronic hypertension. Based on major controlled trials, no evidence exists for acutely lowering blood pressure in such patients and suggests allowing blood pressures in acute stroke to settle spontaneously unless very high.

PATHOPHYSIOLOGY

High blood pressure results in endothelial injury which increases blood-brain barrier permeability leading to brain oedema[6] and mass effects due to raised intra cranial pressure. Intraparenchymal haemorrhages results from smooth muscle cell and endothelial degeneration.

1. In addition, it increases cerebral artery stenosis and increased incidence of embolism arising from the heart and great vessels by accelerating the process of arteriosclerosis.

2. The structural derangements in the resistance vessels leads to increase in peripheral vascular resistance thereby increasing the risk for ischaemic events by compromising on the collateral blood supply.

3. The high blood pressure produces endothelial injury, attracts leucocytes to the site of injury and converts LDL to its oxidized form with smooth muscle proliferation resulting in formation of foam cells, which plays a

central role in atherogenesis and plaque formation and occlusion of the vessel lumen resulting in reduced blood supply distal to the site of occlusion.

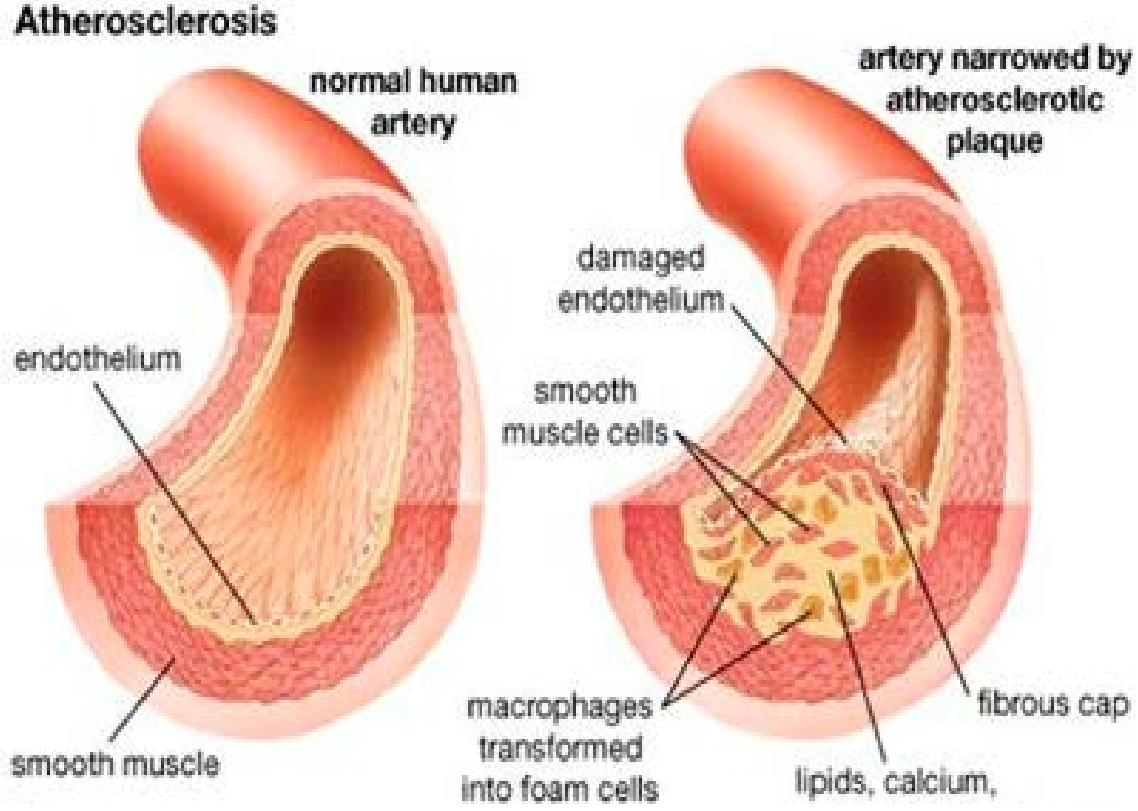

Figure 5 Pathogenesis of Atherosclerosis

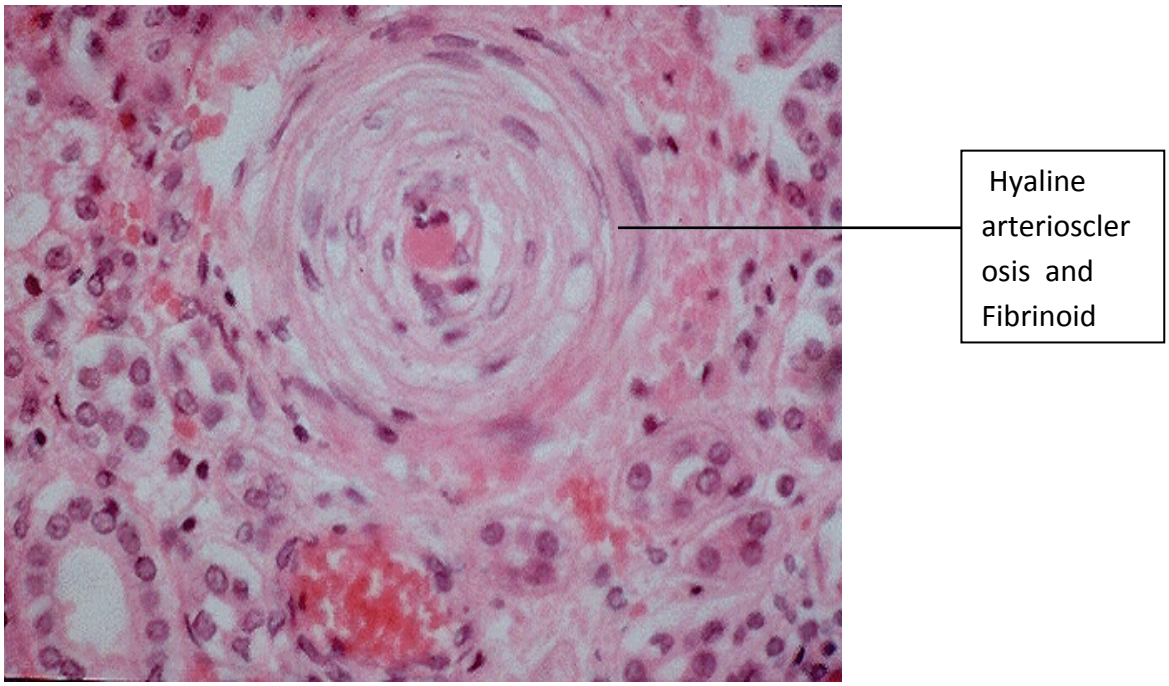

Figure 6 Vascular Changes in Hypertension

INDICATIONS FOR ANTI-HYPERTENSIVE THERAPY IN ACUTE STROKE

For patients with stroke who are not candidates for thrombolytic therapy, the recommended guideline[7] to initiate anti-hypertensive therapy is when blood pressure is above 220/130 mm Hg and if thrombolytic therapy[8] is to be used, the goal blood pressure is <185/110 mm Hg.

For patients presenting with hemorrhagic stroke, therapy can be initiated at blood pressures above 180/130 mm Hg.

In subarachnoid hemorrhage, cautious reduction of blood pressure is indicated when mean arterial pressure is >130 mm Hg.

DIABETES AND STROKE

Diabetes has been proven to be a significant independent risk factor[9] for stroke; the risk in diabetics being 2 to 4 fold greater than in normal population. It is also an important risk factor for morbidity and mortality associated with stroke, with increased incidence of severe neurological deficits and disability[10], higher incidence of stroke recurrence[11-12] and a poorer long-term prognosis.

Diabetes is associated with both microvascular and macrovascular complications affecting several organs including heart,brain, kidneys, skin and muscle. Impaired glucose metabolism in diabetics may favour the initiation of vascular complications through structural derangements mediated by advanced glycation end products and production of reactive oxygen species.

The role of diabetes in stroke has been attributed to the pathophysiological changes seen in the cerebral vessels of patients which includes

1. The pathologic effects of advanced glycation end product accumulation
2. Nitric oxide inhibition leading to impaired vasodilation,
3. Chronic inflammation
4. Smooth muscle cell proliferation,
5. Overproduction of endothelial growth factors,
6. Impaired fibrinolytic activity and

7. Enhanced platelet aggregation

Apart from diabetes being an independent risk factor for stroke, it also increases the incidence of other conventional risk factors which includes hypertension, heart failure, dyslipidemia, and atrial fibrillation.[13]

PATHOGENESIS

Endothelial injury marks the initiation of macrovascular complications in diabetes, with other factors super imposed on it.

Chronic hyperglycemia by inhibiting nitric oxide reduces the vasodilatory response[14] through inhibition of endothelial nitric oxide synthase (eNOS) and increases the production of reactive oxygen species,that leads to further inhibition of eNOS.[15-16.]

In addition, insulin resistance leads to an increase in free fatty acid release from the adipose tissue which in turn stimulates the PKC pathway. And this results in increased ROS generation that further leads to inhibition of eNOS activity. The production of advanced glycosylation end products also inhibits NO production[18] all contributing to impaired vasodilation. Apart from the impaired vasodilatory response, an overproduction of vasoconstrictor substances like endothelin-1 occurs, which has direct vasoconstrictive endothelial effects and indirect fluid volume effects resulting in water and salt retention and the activation of the RAS.

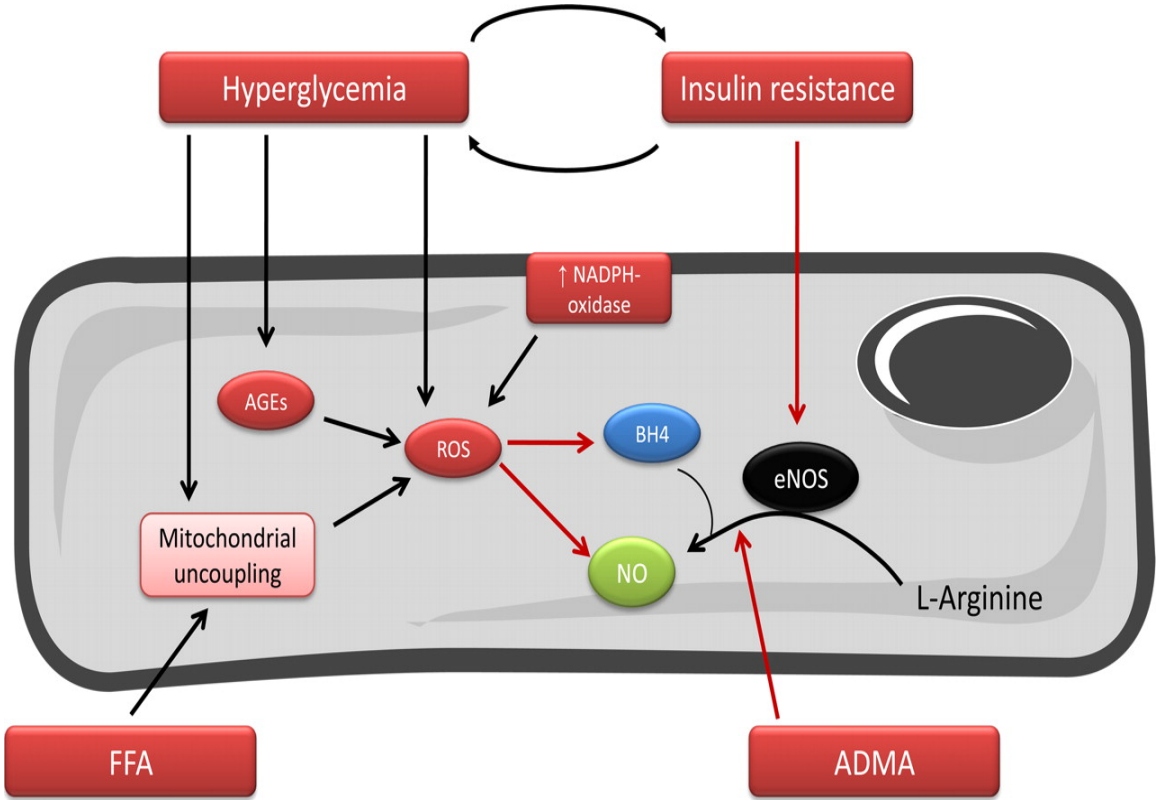

Figure 7 Mechanism of Endothelial dysfunction in diabetes

Impaired platelet function leading to rupture of atherosclerotic plaque[17] and thrombus formation may underlie the pathogenesis of macrovascular complications in diabetes.

Chronic inflammatory state also plays a central role in the development of atherosclerosis related diabetic macrovascular pathology. Endothelial injury results in recruitment of inflammatory cells like monocytes and T lymphocytes which adhere to the injured surface and travel to the intima media of arteries, wherein they engulf oxidized LDL forming foam cells[18] that plays the key role in formation of atherosclerotic plaques.

Smooth muscle cell dysfunction contributes to the structural vessel wall abnormalities seen in diabetes. Following endothelial injury, smooth muscle cells in the tunica media migrate to the intimal layer producing solidification of the atherosclerotic fatty streaks and resulting in an extensive extracellular matrix, thereby weakening the tunica media and resulting in plaque rupture.

A unique effect of diabetes on cerebral vasculature is its effect on neurons and glial cells which occurs during ischemia. This has been explained through the relationship between hyperglycemia and increased intracellular acidosis.[145]

Anaeroic metabolism that occurs during an ischemic event, for instance as in stroke produces neuronal intracellular acidosis which causes nerve cell damage through the mechanism of Reactive Oxygen Species (ROS) production.[19]

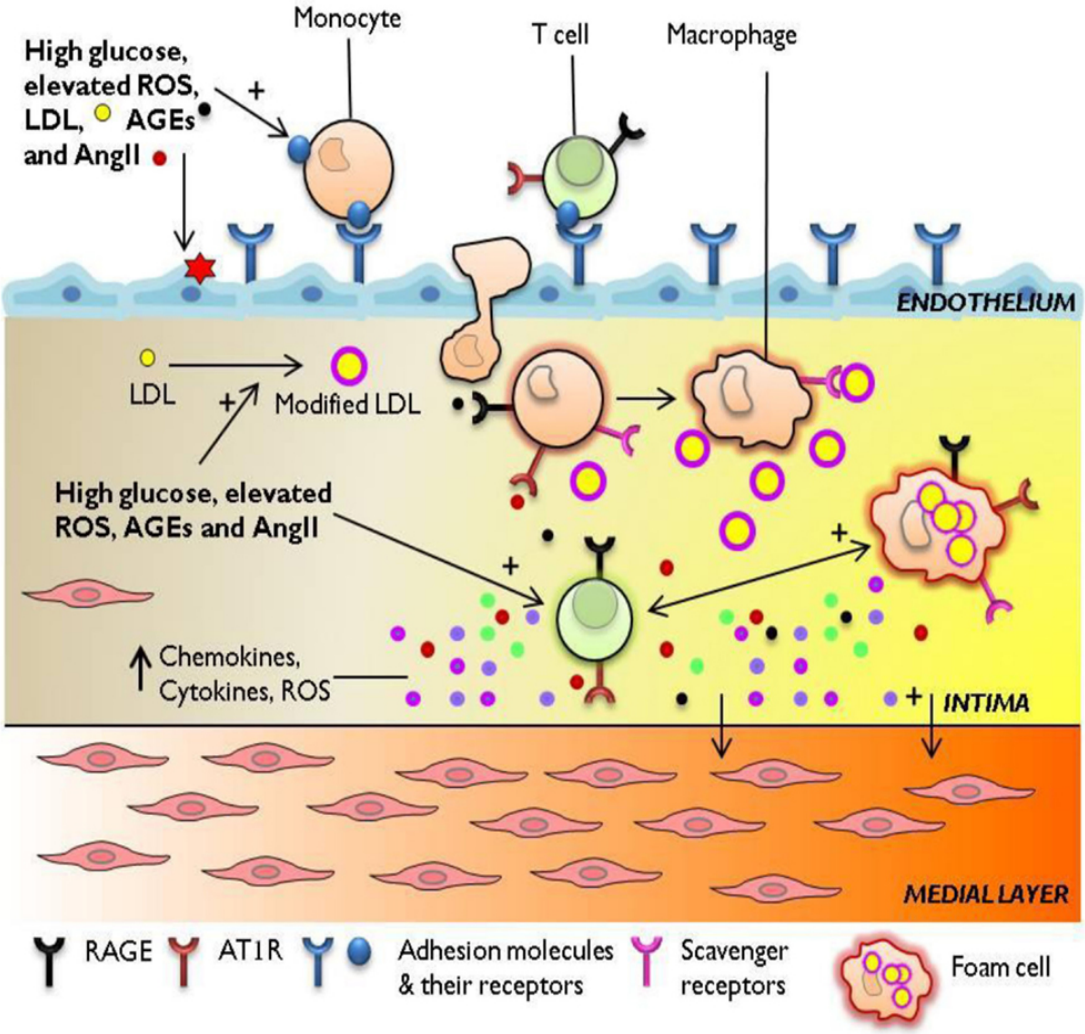

Figure 8 Role of inflammation in atherosclerosis

STROKE AND DYSLIPIDEMIA

Thromboembolism is considered the most common pathology leading to ischaemic stroke, this thromboembolism occurs as a result of atherosclerosis. Nikolai in 1912 was the first to propose the association between cholesterol, and stroke . In what is considered as a breakthrough study in 20th century Nilkolai and his team proved that the obstructive pathology occurring in atheroscelrosis was due to an elevated level of serum cholesterol.

According to recent studies ,apart from elevated LDL other lipids like the reduced levels of HDL-c, increased triglycerides and Apolipoprotein B are also found contributing to the stroke risk. Atherogenic dyslipidemia comprising of reduced HDL-c and an elevated TGL has been proved to be an independent risk factor of increased vascular risk. The MRFIT study conducted on 3,50,977 individuals has proved a positive correlation between total cholesterol levels and risk of ischaemic stroke.[5] Furthermore , its proved that the relative risk for stroke doubles every decade after the age of 55.[8,9]

High density lipoprotein (HDL–c) in reduced concentration ,an independent risk factor of atherosclerosis is also considered a risk for stroke. Numerous prospective studies have proved a significant reduction in non fatal stroke in subjects with an elevated or normal HDL-c levels[10]. The levels of HDL-c were inversely correlated with atheroma burden. The plasma levels of triglyceride has no independent predictive value in stroke risk.

Lipoproteins- no concrete evidence exists pointing to the connection between stroke risk and lipoprotein levels. There are controversial studies denoting the association between lipoprotein–a and stroke incidence[20].the association between the levels of Apo E and the cerebrovascular risk is also under study. Few other studies indicate the positive predictive capacity of Apo B , and Apo A1 in cerebrovascular events.

Further, treatment of dyslipidemia is associated with significant risk reduction in stroke. According to the CARE[25] ,PROSPER ,ASCOT trials there is a proven in reduction in stroke risk by 31 %, on treatment with statins aimed at reducing LDL levels.

STROKE AND HEART DISEASES

Cardioembolic stroke results when a thrombus within the heart chambers breaks and dislodges embolic fragments into the vessel wall. Sometimes an emboli may originate from the distal end of a thrombus intraarterially, in a severely stenosed or occluded carotid or vertebral artery or from large atheromatous plaques in the aorta.

Arrhythmias such as atrial fibrillation, secondary to valvular heart diseases or ischemic heart disease and atrial myxoma also predispose to embolic stroke. Thrombotic or infected material e.g. as in infective endocarditis which adheres to the aortic or mitral heart valves and clots originating on prosthetic heart valves also break free to produce embolic stroke.

Ischemic infarction results when the embolus becomes arrested at a bifurcation or at the site of natural narrowing of the lumen of an artery. The infarction may be pale, hemorrhagic or mixed; hemorrhagic infarction mostly always indicates embolism as does venous occlusion. Any region of the brain may be affected with the territories of the middle cerebral artery, especially the superior division, being the most frequently involved. Large embolic clots can

block large vessels like the carotids in the neck, while tiny fragments may reach vessels as small as 0.2 mm in diameter, usually with minimal effects.

As embolic strokes develops rapidly, collateral blood supply does not become established and hence sparing of the brain territory distal to the site of occlusion as seen in slowly developing thrombotic strokes is usually not evident.

The most common cause of an embolic stroke being a chronic or recent atrial fibrillation, it usually arises from a mural thrombus within the atrial appendage.

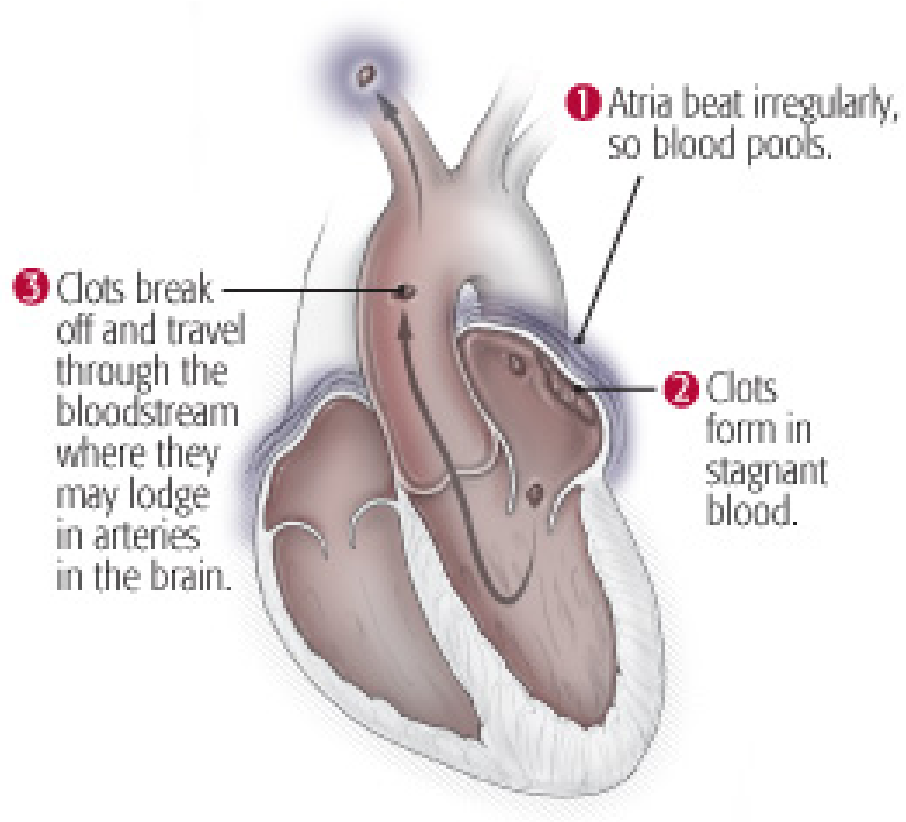

Figure 9 Embolic Stroke in Atrial Fibrillation

Based on the Framingham Heart Study, patients with chronic atrial fibrillation are approximately 6 times more prone to stroke than an age-matched population with normal cardiac rhythm (Wolf et al, 1983) and the risk is higher if rheumatic valvular heart disease is also present.

Furthermore, the risk for stroke in patients with atrial fibrillation varies with age, being 1 percent per year in persons younger than age 65 years, and as high as 8 percent per year in those older than age 75 years with additional risk factors. These play a significant role in determining the benefit of chronic anticoagulation therapy.

Embolism also occurs in cases of paroxysmal atrial fibrillation or flutter. Post myocardial infarction, mural thrombus formed on the damaged endocardium in the left ventricle, particularly if there is an aneurysmal sac, is an important source of cerebral emboli.

Emboli mostly tend to occur in the first few weeks after an acute myocardial infarction but Loh and colleagues found that a lesser degree of risk persists even upto 5 years. Cardiac catheterization or surgery, especially valvuloplasty, may disseminate fragments from a thrombus or a calcified valve. Mitral and aortic valve prostheses are also additional important sources of embolism.

STROKE AND TOBACCO USE

Smoking as an independent risk factor has been known to double the risk of ischemic stroke. Cigarette smoke is generally divided into two phases which include a tar phase (particulate phase) and a gas phase. When passed through the Cambridge glass-fiber filter, the material that gets trapped is the tar phase with a particulate material of size >0.1µm. While the material that passes through the filter comprises the gas phase.

The particulate phase of cigarette smoke contains more than 10^{17} free radicals/g, and gas phase contains more than 10^{15} free radicals/puff .The radicals related to the particulate phase have a longer life span (hours to months) where as those associated with gas phase are short lived(seconds). It is found that amidst all the identified constituents, nicotine found in the particulate phase, is the addictive substance in cigarette smoke.

Active smoking as well as passive smoking has been found to be related to a constant increase in carotid artery intimal-medial thickness. By modifying the activity of the endothelial NO synthetase enzyme and inhibiting nitric oxide production cigarette smoking impairs the vasodilation in macrovascular as well as in microvascular beds. Apart from serving a vasoregulatory function[21] NO also it plays a vital role in regulating inflammation by preventing leukocyte adhesion as well as platelet activation. Hence, an alteration in NO production hastens the process of atherosclerotic events.

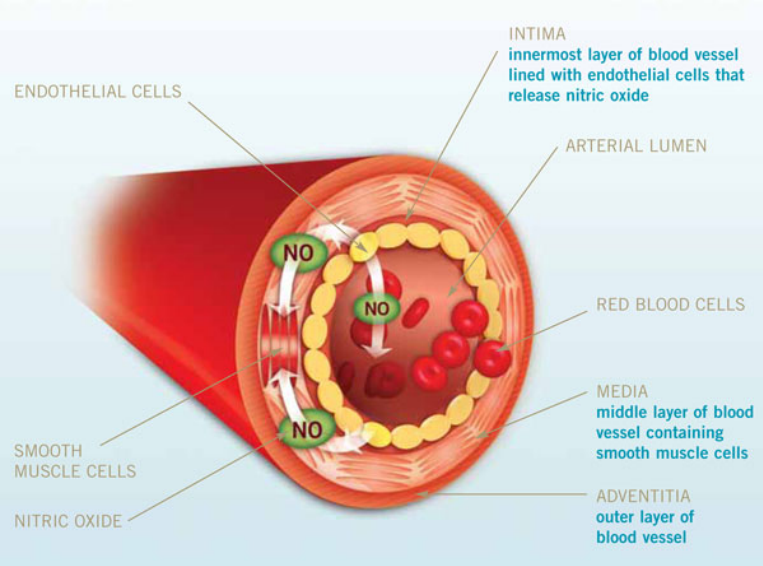

Figure 10 Role of Nitric Oxide in Endothelial vasodilation

SMOKING AND INFLAMMATION

The inflammatory response plays a central role in the instigation and progression of atherosclerosis. Based on various studies, evidence exists about smoking causing a significant increase in the peripheral leukocyte count. Inflammatory markers like C-reactive protein, interleukin-6, and tumor necrosis factor- alpha(TNF-α) have also been found to be significantly increased in smokers [22].

Elevation of several proinflammatory cytokines increases leucocyte endothelial cell interaction leading to atherogenesis and recruitment of leucocytes which is the early event in the pathogenesis of atherosclerosis. It was found that the soluble adhesion molecules such as ICAM-1, VCAM-1 and

E-Selectin levels were higher in smokers than non smokers. It also activates proatherogenic molecules resulting in alteration in cell-cell interactions and helps in hastening the process of atherosclerosis.

Smokers have higher serum total cholesterol, LDL and triglyceride levels and lower levels of HDL. The triglyceride and high-density lipoprotein abnormalities have been found to be linked to insulin resistance.

It increases oxidation of LDL molecules by decreasing the activity of paraoxonase, an enzyme that inhibits LDL oxidation.

TREATMENT: ACUTE ISCHEMIC STROKE

After the clinical diagnosis of stroke is made, an orderly process of evaluation and treatment should follow. The first goal is to prevent or reverse brain injury. Attend to the patient's airway, breathing, circulation (ABC's). Perform an head CT scan to differentiate between ischemic stroke and hemorrhagic stroke.

Medical Support

When ischemic stroke occurs, the immediate goal is to optimize cerebral perfusion in the surrounding ischemic penumbra. Attention is also directed toward preventing infections (pneumonia, urinary, and skin) and deep venous thrombosis (DVT) with pulmonary embolism.

Because collateral blood flow within the ischemic brain is blood pressure dependent, there is controversy about whether blood pressure should be lowered acutely. Blood pressure should be lowered if there is malignanthypertension or if blood pressure is >185/110 mm Hg and thrombolytic therapy is anticipated. Fever is detrimental and should be treated with antipyretics and surface cooling. Serum glucose should be monitored and kept at <6.1 mmol/L (110 mg/dL) using an insulin infusion if necessary.

The larger the infarct, the greater the likelihood that clinically significant edema will develop. Water restriction and IV mannitol may be used to raise the serum osmolarity, but hypovolemia should be avoided as this may contribute to hypotension and worsening infarction.

Intravenous Thrombolysis

The NINDS study used IV rtPA (0.9 mg/kg to a 90-mg max, 10% as a bolus, then the remainder over 60 minutes) versus placebo in patients with ischemic stroke within 3 hours of onset. One-half of the patients were treated within 90 minutes. Thus, despite an increased incidence of symptomatic intracerebral hemorrhage, treatment with IV rtPA within 3 hours of the onset of ischemic stroke improved clinical outcome.

Use of IV tPA is now considered a central component of primary stroke centers as the first treatment proven to improve clinical outcomes in ischemic

stroke and is cost-effective and cost-saving. The time of stroke onset is defined as the time the patient's symptoms began or the time the patient was last seen as normal. Patients who awaken with stroke have the onset defined as when they went to bed.

Antithrombotic Treatment

Platelet Inhibition

Aspirin is the only antiplatelet agent that has been proven effective for the acute treatment of ischemic stroke; there are several antiplatelet agents proven for the secondary prevention of stroke. Use of aspirin within 48 hours of stroke onset reduced both stroke recurrence risk and mortality minimally. The glycoprotein IIb/IIIa receptor inhibitor abciximab was found to cause excess intracranial hemorrhage and should be avoided in acute stroke. Clopidogrel is being tested as a way to prevent stroke following TIA and minor ischemic stroke.

Lipid Lowering drugs

Statins are used after an episode of cerebro vascular accident by reducing the lipid levels helps in delaying the further progression of atherosclerosis and stabilizes the plaque preventing its rupture and thrombus formation.

HYPOTHYROIDISM

THYROID: ANATOMY AND DEVELOPMENT

The thyroid gland derives its origin from the greek word ‘thyreos’ denoting shield and it comprises of two lobes joined by an isthmus. It lies in front of the trachea extending from the cricoid cartilage to the suprasternal notch. The gland is highly vascular, soft in consistency and weighs around 12–20 g. The thyroid gland develops from the floor of the pharynx and migrates along the thyroglossal duct to reach its final location in the neck. Thyroid hormone synthesis begins as early as around 11 weeks gestation. The hormones secreted by the thyroid gland play a key role in cell differentiation during development and helps to maintain thermogenic and metabolic homeostasis in the adult

Thyroid gland development is due to the coordinated expression of several developmental transcription factors like thyroid transcription factor (TTF)-1, TTF-2, and paired homeobox-8 (PAX-8) which are expressed selectively in the thyroid gland. These factors are also responsible for induction of thyroid-specific genes such as thyroglobulin (Tg), thyroid peroxidase (TPO), the sodium iodide symporter (Na^+/I, NIS), and the thyroid-stimulating hormone receptor (TSH-R). Occurrence of mutation in these transcription factors or their target genes are rare causes of thyroid agenesis or dyshormonogenesis,

though in most cases,etiology of congenital hypothyroidism remains unknown.

The thyroid gland consists of numerous spherical follicles that contain colloid rich in thyroglobulin, which is essential for thyroid hormones synthesis.

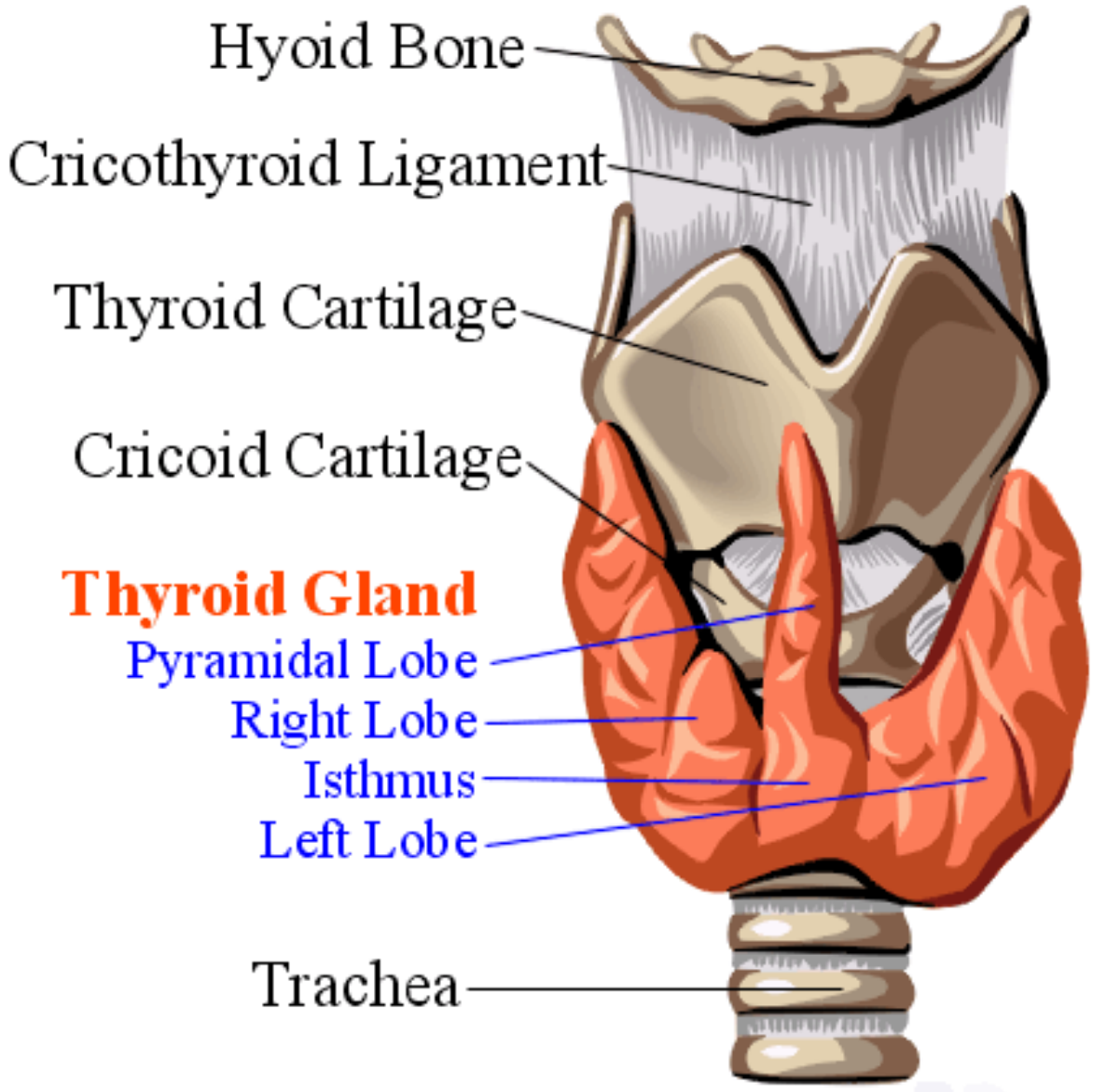

Figure 11 Thyroid Gland

REGULATION OF THYROID AXIS

Thyroid stimulating hormone(TSH), secreted by the thyrotrope cells of the anterior pituitary is a 31-kDa hormone composed of α and β subunits; the α subunit which shares similarity to many other glycoprotein hormones [luteinizing hormone, follicle-stimulating hormone, human chorionic gαonadotropin], whereas the β subunit is unique to TSH.

The thyrotropin releasing hormone (TRH) from the hypothalamus stimulates the pituitary production of TSH which stimulates thyroid gland to produce the thyroid hormones T_3 and T_4. Thyroid hormones, acting predominantly through thyroid hormone receptor β 2, sends feed back to pituitary and hypothalamus to inhibit TSH and TRH respectively.

Like other pituitary hormones, TSH is the main regulator of this endocrine feedback loop mechanism. TSH is measured using immunoradiometric assays which are highly sensitive and specific. And TSH can be used for the diagnosis of hyperthyroidism (low TSH) as well as hypothyroidism (high TSH). Drugs like dopamine, glucocorticoids and somatostatin when administered exogenously suppress TSH function.

Reduced levels of T_3 and T_4 enhance TSH production whereas higher levels suppress TSH levels, thereby underscoring the importance of these hormones in the regulation of TSH production.

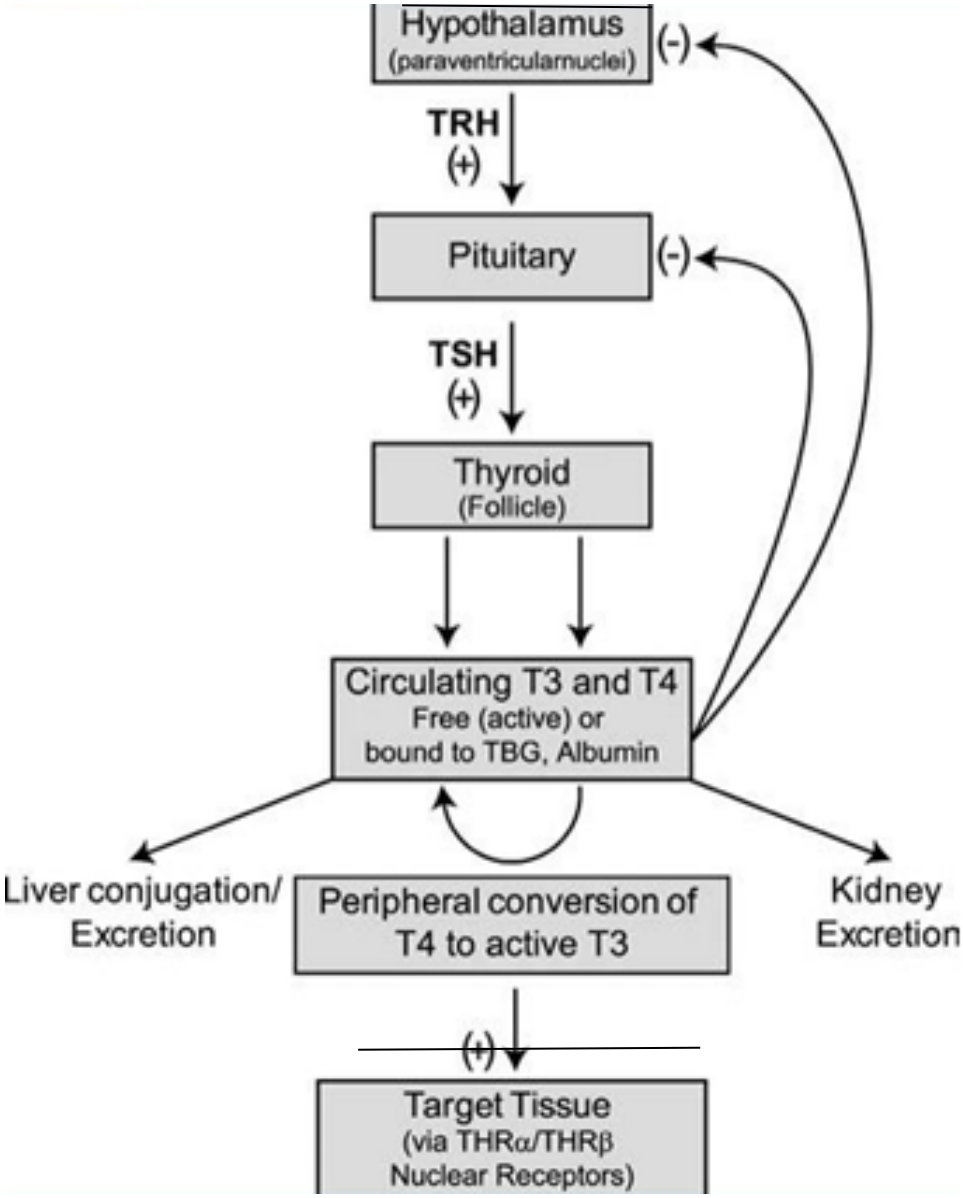

Figure 12 Hypothalamo-pituitary-thyroid axis.

THYROID HORMONE SYNTHESIS AND FUNCTION

Iodine Metabolism and Transport

The first critical step in thyroid hormone synthesis is Iodine uptake[23]. Iodine from diet is carried by serum binding proteins, particularly albumin from where it is taken into thyroid follicular cells by NIS(sodium iodide symporter) expressed at its basolateral membrane.

Adaptations to variations in dietary intake of iodine is highly regulated by this symporter function and expression. One of the rare causes of congenital hypothyroidism is mutation of the *NIS* gene.

Based on urinary excretion data, iodine deficiency is more prevalent in many mountainous regions, central Africa, central South America and northern Asia and it remains the most common cause of preventable mental deficiency .There is an increased prevalence of goiter in areas of relative iodine deficiency and when it becomes more pronounced results in cretinism in children,characterised by mental and growth retardation and wide range of cognitive dysfunction and metabolic disturbances in adults.

Organification, Coupling, Storage, Release

Following uptake into follicular cells, iodine is oxidized in an organification reaction catalysed by TPO and hydrogen peroxide and is added to selected tyrosyl residues within Tg to form diiodotyrosine(DIT) and monotyrosine(MIT).These are further coupled via an ether linkage involving thyroperoxidase(TPO) with coupling of two molecules of DIT or one of DIT and one of MIT leading to formation of T_4 and T_3, respectively. Reuptake of Tg into the thyroid follicular cell allows proteolysis and the release of newly synthesized T4 and T_3.

Uncoupled mono- and diiodotyrosines (MIT, DIT) are deiodinated by the enzyme dehalogenase, thereby recycling any iodide that is not converted into thyroid hormones.

In most cases of congenital hypothyroidism,the etiology remains unknown while rare causes have been attributed to recessive mutations in TPO or Tg mainly, but defects have also been identified in the TSH-R, NIS, pendrin, hydrogen peroxide generation, and dehalogenase.

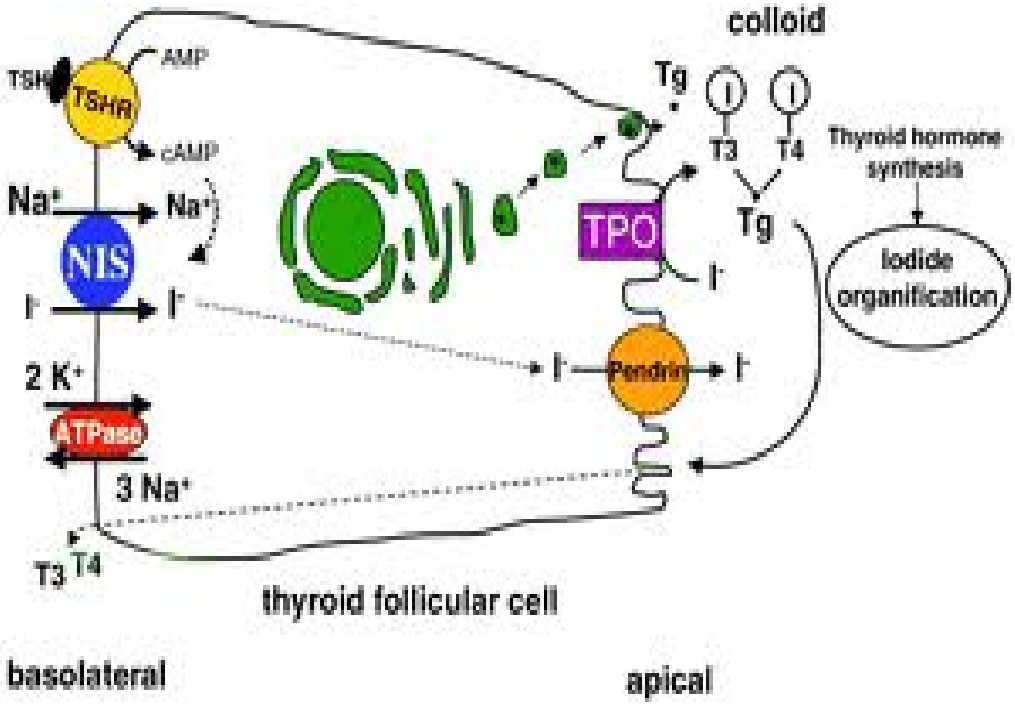

Figure 13 Thyroid Hormone Synthesis

TSH Action

TSH regulates thyroid gland function through the TSH-R, a seven-transmembrane G protein–coupled receptor (GPCR) that is coupled to the subunit of stimulatory G protein (G_s), which activates adenylyl cyclase, leading to increased production of cyclic AMP. Recessive loss-of-function mutations causes thyroid hypoplasia and congenital hypothyroidism and dominant gain-of-function mutations cause sporadic or familial hyperthyroidism that is characterized by goiter, thyroid cell hyperplasia, and autonomous function

Other Factors that Influence Hormone Synthesis and Release

Apart from TSH being the prime hormonal regulator of thyroid function, a variety of growth factors also influence thyroid hormone synthesis. These include insulin-like growth factor I (IGF-1), epidermal growth factor, transforming growth factor (TGF-), endothelins, and various cytokines. In individuals with a normal thyroid, the gland escapes from inhibitory effect of excess iodide, however the suppressive action of high iodide may persist in patients with underlying autoimmune thyroid disease.

Serum Binding Proteins

T4 is secreted in about twentyfold excess over T_3 and both hormones are bound to plasma proteins, including thyroxine-binding globulin (TBG), transthyretin (TTR, formerly known as thyroxine-binding prealbumin, or TBPA), and albumin. These proteins by increasing the circulating pool and delaying clearance modulate hormone delivery to selected tissue sites.

Characteristics of Circulating T_4 and T_3		
Hormone Property	**T_4**	**T_3**
Serum concentrations		
Total hormone	8 g/dL	0.14 g/dL
Fraction of total hormone in the free form	0.02%	0.3%
Free (unbound) hormone	21×10^{-12}M	6×10^{-12}M
Serum half-life	7 d	0.75 d
Fraction directly from the thyroid	100%	20%
Production rate, including peripheral conversion	90 g/d	32 g/d
Intracellular hormone fraction	20%	70%
Relative metabolic potency	0.3	1
Receptor binding	10^{-10}M	10^{-11}M

Table 1: Characteristics of Circulating T_4 and T_{3s}

Despite its low serum concentration,TBG carries about 80% of the bound hormones due to its high affinity for thyroid hormones. Whereas albumin with a high plasma concentration has relatively low affinity for thyroid hormones and it binds up to 10% of T_4 and 30% of T_3. TTR carries about 10% of T_4 but little T_3.

Approximately 99.98% of T4 and 99.7% of T_3 are protein-bound and since T_4 is more avidly bound to plasma proteins than T_3, the proportion of

unbound T_3 > unbound T_4, but there is less unbound T_3 in the circulation as it is produced in smaller amounts and cleared more rapidly than T_4

Nuclear Thyroid Hormone Receptors

Thyroid hormones[24] bind with high affinity to nuclear *thyroid hormone receptors* (TRs) α and β..The receptors bind as heterodimers with retinoic acid X receptors (RXRs) and then to specific DNA sequences, termed *thyroid response elements* (TREs), in the promoter regions of target genes. The activated receptor then in turn can stimulate gene or inhibit transcription depending on the nature of the regulatory elements in the target gene.

Though T_4 is produced in excess of T_3, receptors are occupied mainly by T_3 owing to their high affinity and greater plasma availability resulting in maximum hormonal potency. After binding to TRs, thyroid hormone induces conformational changes in the receptors leading to alteration in gene expression.

Laboratory Evaluation

Measurement of Thyroid Hormones

The immunochemiluminometric assays (ICMAs) for TSH are specific and sensitive enough to detect very low levels of TSH (0.1 mU/L). The first step in evaluating thyroid dysfunction is to measure TSH levels as suppressed, normal or high in response to alterations in levels of T_3 and T_4. This is followed

by measurements of serum T_3 and T_4 levels to make a diagnosis of hypo (with elevated TSH) or hyperthyroidism (with suppressed TSH levels).

As total T_4 and T_3 are highly protein-bound and influenced by numerous factors like illness, medications and genetic factors it is useful, therefore, to measure the free, or unbound, hormone levels, which reflects the biologically active hormone pool.

Total T_4 and T_3 levels are elevated when TBG is increased due to estrogens (pregnancy, oral contraceptives, hormone therapy, tamoxifen), and decreased when TBG binding is reduced (androgens, nephrotic syndrome). As total T_4 and T_3 are highly protein-bound and influenced by numerous factors like acute illness, genetic disorders and various medications (phenytoin, carbamazepine, salicylates, and NSAIDs)which can interfere with thyroid hormone binding, it is preferable to measure the free, or unbound, hormone levels, which remains normal under such situations.

In certain cases,TSH as a screening test without simultaneous unbound T4 determinations may be misleading. Although hypothyroidism is the most common cause of an elevated TSH level, rare causes include a TSH-secreting pituitary tumor, thyroid hormone resistance, and assay artifact. Conversely, a suppressed TSH level usually indicates thyrotoxicosis but may also be seen during the first trimester of pregnancy ,after treatment of hyperthyroidism and

on exposure to certain drugs like dopamine or high doses of steroids.

The most common antibodies detected in patients with auto immune thyroid disease is antibodies against TPO and Tg.

Hypothyroidism

Iodine deficiency remains the most common cause of hypothyroidism worldwide. In areas of iodine sufficiency, autoimmune disease and iatrogenic causes are the most common causes.

Symptoms	**Signs**
Tiredness, weakness	Puffy face, hands, and feet (myxedema)
Dry skin	Diffuse alopecia
Feeling cold	Dry coarse skin
Hair loss	Decreased heart rate
Difficulty concentrating and poor memory	Carpal tunnel syndrome
Constipation	Delayed tendon reflex relaxation
Weight gain with poor appetite	Serous cavity effusions
Dyspnea	
Hoarse voice	
Menstrual disturbances	

Table 2: Signs and Symptoms of Hypothyroidism

Autoimmune Hypothyroidism

Classification

Autoimmunity is the most common cause of hypothyroidism which may be either associated with a goiter (Hashimoto's thyroiditis) or resulting in atrophy of the thyroid gland. As auto immunity progresses and reduces thyroid function, there is a compensatory rise in TSH levels to maintain normal thyroid hormone levels. With most of the patients being asymptomatic, this is termed subclinical hypothyroidism. It progresses to overt hypothyroidism when patients become symptomatic with reduced T4 levels, and a compensatory rise in TSH levels >10 mIU/L.

Prevalence

The mean annual incidence rate of autoimmune hypothyroidism is up to 4 per 1000 women and 1 per 1000 men. It is found to be more prevalent in Japanese populations due to genetic factors and intake of high iodine diet. Subclinical hypothyroidism is found in 6–8% of women and 3% of men. When subclinical hypothyroidism is associated with positive TPO antibodies, the annual risk of developing clinical hypothyroidism rises to 4%.

Pathogenesis

In Autoimmune thyroiditis[25], there is lymphocytic infiltration of the gland, by CD4+ and CD8+ T cells resulting in atrophy and fibrosis of thyroid gland. CD8+ cytotoxic T cells mediate destruction by either perforin-induced cell necrosis or granzyme B–induced apoptosis.

Genetic and environmental factors contribute to the development of autoimmune thyroid disorders, of which HLA-DR polymorphisms are the most widely recognized.

By its direct toxic effects or through immune mediated mechanisms, high iodine intake increases the risk of autoimmune hypothyroidism.

Antibodies to TPO and Tg serve as the most clinical useful markers of thyroid autoimmunity. Up to 20% of patients with autoimmune hypothyroidism have antibodies against the TSH-R which prevent the binding of TSH, resulting in hypothyroidism and especially in Asian patients, thyroid atrophy. This is in contrast to TSI, which does not stimulate the receptor and results in hypothyroidism.

Clinical Manifestations

The skin is dry, coarse with decreased sweating, thinning of the epidermis and hyperkeratosis of the stratum corneum. Increased dermal glycosaminoglycan content traps water, giving rise to skin thickening without pitting (*myxedema*). A puffy face with edematous eyelids and nonpitting pretibial edema gives a typical picture of hypothyroid patients. The hair becomes dry, brittle and falls out easily resulting in diffuse alopecia, with thinning of the outer third of the eyebrows, though not specific for hypothyroidism. Nail growth retardation is also a common finding.

Other common features include constipation and increase in weight which is due to fluid accumulation in the subcutaneous tissues. Decreased libido, reduced fertility and increased incidence of miscarriage is common which may be due to increased Prolactin levels. There may be oligomenorrhea or amenorrhea in long-standing disease, but menorrhagia is also common.

Cardiovascular changes includes decreased myocardial contractility and pulse rate, leading to a reduced stroke volume and bradycardia and pericardial effusions (around 30%) which do not compromise cardiac function are also common. Increased peripheral resistance may contribute to the development of diastolic hypertension. Fluid may also accumulate in other serous cavities and in the middle ear, giving rise to conductive deafness. Though pulmonary function

remains normal, dyspnea may be caused by pleural effusion, impaired respiratory muscle function, diminished ventilatory drive, or sleep apnea.

On examination, there may be slow relaxation of tendon reflexes and pseudomyotonia. Cognitive disturbances include memory disturbances and poor concentration.

DEFINITION OF SUBCLINICAL AND OVERT HYPOTHYROIDISM

Overt hypothyroidism is diagnosed in patients who have symptoms of hypothyroidism, reduced levels of thyroid hormones T_3, T_4 and elevated TSH (> 10μIU/ml) whereas a diagnosis of subclinical hypothyroidism is made when T_3, T_4 levels are within the normal range with mild elevations of TSH levels (<10μIU/ml) which act to maintain normal thyroid hormones but can eventually progress to overt hypothyroidism, when the compensatory mechanism is overwhelmed by the auto immune process.

HYPOTHYROIDISM AND ENDOTHELIAL DYSFUNCTION

The vascular homeostasis is maintained by the endothelium by a balance in the production of vasoconstrictor and vasodilator substances[26]. Nitric oxide, the most important vasodilator substance is produced by the endothelium during conversion of L-arginine into citrulline catalysed by the enzyme nitric oxide synthase.

In presence of increased serum cholesterol levels, due to increased oxidative stress the endothelium causes breakdown of nitric oxide production.In addition, endothelial dysfunction is also influenced to a major extent by other risk factors like aging, hypertension, smoking and post menopausal status.So dyslipidemia acts as an independent risk factor for altering endothelial function and in patients with subclinical hypothyroidism (SH) having abnormal lipid profile, this could play a role in mediating endothelial dysfunction.

Evidence from a study conducted on patients with SH studied the vasodilating effect in response to acetylcholine and it was found to be significantly reduced in patients with SH compared to euthyroid controls. And it was also found to be impaired in patients with SH whose total serum cholesterol levels were in the normal range.This clearly indicates the direct effect of thyroid hormones as an independent risk factor in producing endothelial dysfunction in SH patients apart from the contributory effects of lipid abnormalities on endothelial function and NO production.

In addition to this, the effect of autoimmunity and inflammation seen in hypothyroid patients may play a role. Most patients with subclinical hypothyroidism had evidence of autoimmune thyroiditis as documented by TPO autoantibodies. In the above study conducted to determine the effects of SH on endothelial function, Erythrocyte Sedimentation Rate (ESR) was measured and was found to be significantly raised and this contributes to the confirmation of

hypothesis that inflammation present in autoimmune thyroid disorders could also play a part in mediating impaired endothelial vasodilation.

But more specific inflammatory markers like C-Reactive Protein and interleukins need to be studied to confirm this hypothesis as ESR is a non specific inflammatory marker found to be raised in various other pathologies.

In patients with SH, lipoprotein a values were also found to be elevated and has a significant co-relation with endothelial dysfunction in coronary circulation thereby contributing to coronary artery disease.

So all these factors in patients with subclinical hypothyroidism including thyroid dysfunction, chronic inflammatory state seen in autoimmune thyroid disorders and altered lipid metabolism leading to hypercholesterolemia could jointly contribute to the impaired endothelium dependent vasodilation seen in these patients.

This is also supported by the fact that treatment of SH with L-Thyroxine was found to restore an euthyroid state and an improvement in acetylcholine induced vasodilation and NO availability. On receiving replacement therapy, TSH levels were reduced, there was a decrease in serum total and LDL cholesterol levels and no significant changes in lipoprotein a levels.

So to conclude, subclinical hypothyroidism represents an early, independent, reversible risk factor in causing endothelial dysfunction in addition to the co-existing lipid abnormalities seen in SH patients. This highlights the importance of early replacement therapy in not only delaying the progression to overt hypothyroidism but also in restoring endothelium dependent vasodilation, reversal of lipid abnormalities and slowing down the atherogenic process and its associated complications.

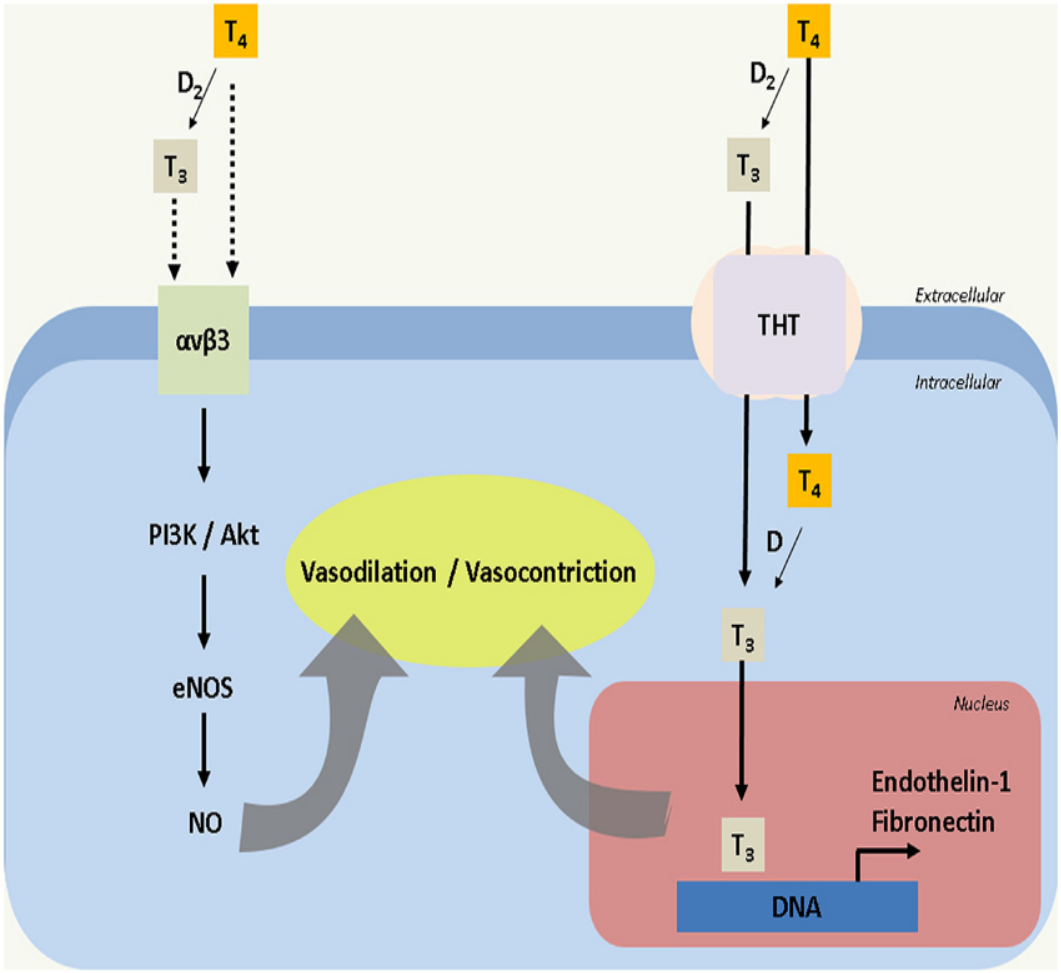

Figure 14 Thyroid hormone in Endothelial vasodilation

HYPOTHYROIDISM AND DYSLIPIDEMIA:

Conventionally, subclinical and overt hypothyroidism is associated with elevation of total serum and low density lipoprotein (LDL) cholesterol levels and normal or elevated high density lipoprotein (HDL) cholesterol levels.[27] Overt and subclinical hypothyroidism is associated with reduced levels of total LDL and HDL cholesterols.[28] These alterations in lipid metabolism are mainly due to the effect of thyroid hormones in regulating the activity of the enzymes involved in metabolism of the lipoproteins.

ACTION OF THYROID HORMONES IN LIPID METABOLISM

To be more specific, the thyroid hormones regulates the activity of the enzyme 3 - hydroxyl – 3 – methyl glutaryl – coenzyme A (HMG – CoA) which forms the first step in cholesterol synthesis by catalyzing the conversion of HMG - CoA to mevalonate and resulting in elevation of cholesterol levels.

The thyroid hormones have a key role in activating the LDL receptors, the binding of the thyroid hormones to the promoter region of the LDL receptor gene which contains a thyroid hormone responsive element (TRE) that allow the T_3 levels in **upregulating the gene expression of LDL receptors.**[29]

Thyroid hormones also stimulate the enzyme cholesteryl ester transfer protein (CETP) that transports cholesteryl esters from HDL_2 to the triglycerides

and very low density lipoproteins (VLDL) in the opposite direction.[30] In addition, these hormones also stimulate the enzyme lipoprotein – lipase (LPL) that is involved in the metabolism of TGL rich lipoproteins and hepatic lipase (HL) an enzyme which converts HDL_2 to HDL_3.[31]

Therefore disturbancess in thyroid function can result in changes in composition and transport of lipoproteins.[32] With declining thyroid function, the levels of total serum and LDL cholesterol are elevated, thereby making hypothyroidism an important cause of secondary dyslipidemia.[33]

LIPID PROFILE IN OVERT HYPOTHYROIDISM

Despite lower cholesterol synthesis due to reduced activity of HMG – COA reductase enzyme in hypothyroidism, there is an increase in total serum cholesterol levels due to raised levels of LDL and intermediate density lipoprotein (IDL) cholesterol.

The main reason for elevated cholesterol levels i.e, the increase in LDL and IDL cholesterol concentration in hypothyroidism is mainly due to **down regulation of LDL receptors** leading to decreased receptor mediated catabolism of LDL and IDL.[34]

Though not very commonly found, there is also decreased activity of lipoprotein lipase which metabolises triglyceride rich lipoproteins (VLDL)

hence associated with increased TGL and VLDL levels. The VLDL and IDL particles in hypothyroid patients are rich in cholesterol and apolipoprotein E resembling the lipid profile in type III hyperlipoproteinemia.[35] Hence in patients who are homozygous for apolipoprotein E 2 allele if super imposed with an insult to the thyroid may develop full blown features of type III hyperlipoproteinemia.

Mechanism of increase in HDL Cholesterol levels

There is an increase in HDL cholesterol levels mainly due to increased concentration and also due to decreased catabolism of of HDL_2 particles[36] owing to the decreased activity of HL enzyme. There is reduced transfer of cholestryl esters from HDL to VLDL due to decreased activity of CETP also increasing the HDL cholesterol levels.[37]

HYPOTHROIDISM AND ATHEROSCLEROSIS

There are a number of mechanisms leading to development of atherosclerosis in hypothyroidism

1. T_4 has three specific binding sites on apolipoprotein B and inhibits LDL oxidation invitro.[38] So hypothyroidism favors LDL oxidation[39].
2. Hypothyroidism is associated with increase in serum homocysteine levels.[40]

3. Through sympathetic and adrenaline activation[41] and increased peripheral resistance leading to vessel wall (aortic) stiffness produces diastolic hypertension.[42]
4. The decrease in thyroid hormones also favors a hypercoagulable state.[43]

EVIDENCE SUPPORTING THE ROLE OF HYPOTHYROIDISM IN DYSLIPIDEMIA

The lipid abnormalities seen in hypothyroidism has been found to be significantly reduced with L thyroxine (T_4) supplementation and also increases previously low biliary cholesterol excretion.[44] It usually takes around 4 to 6 weeks of thyroxine supplementation to correct lipid abnormalities in overt hypothyroidism. Despite restoring an euthyroid status, the failure of substitution therapy to normalise the lipid abnormalities should take into account any superimposed dyslipidemia[45].

1. According to a recent meta analysis after initiating substitution therapy there is a decrease in serum total and LDL cholesterol levels to 7.9mg/dl and 10mg/dl respectively.[46] In patients with higher cholesterol levels prior to treatment and in hypothyroid patients taking sub optimal T_4 doses this reduction in cholesterol levels was significantly high.[47]
2. Serum lipoprotein a levels were also found to reduce with thyroxine supplementation.[48]

3. Though a less consistent finding serum HDL cholesterol levels were also found to decrease with L – thyroxine (T_4) therapy.[48]
4. So in total there is a significant decrease in serum total and LDL cholesterol, lipoprotein a, apolipoprotein B but such significant changes were not seen with HDL cholesterol, triglycerides and apolipoprotein AI.[49]

In patients with dyslipidemia prevalence of overt hypothyroidism is not low.[50]

LIPID PROFILE IN SUBCLINICAL HYPOTHRYOIDISM

Normal levels of T_3 and T_4 with mildly elevated serum TSH levels up to 10µIU/ml defines subclinical hypothyroidism (SH). In comparison to overt hypothyroidism subclinical hypothyroidism is more common and has a higher prevalence in women and elderly.[51] It was found that in patients with positive anti thyroid anti bodies but with high normal TSH levels (2-4µIU/ml) there was increase in total serum cholesterol.

In comparison with euthyroid controls, patients with subclinical hypothyroidism have increased serum total and LDL cholesterol[52], apolipoprotein B and lipoprotein a – Lp(a). But the levels of HDL cholesterol, triglycerides and apolipoprotein AI were not found to be significantly increased.[53]

In patients with antibodies to thyroid peroxidase (TPO) as well as in smokers, subclinical hypothyroidism has been associated with increased risk of coronary events owing to the lipid abnormalities seen in SH.[54] Subclinical hypothyroidism impairs endothelial vasodilation by decreasing heart rate variability, ventricular function as well as cardio vascular adaptation to effort. In women with SH, smoking acts as an additional risk factor in altering the lipid profile and aggravating thyroid failure jointly contributing to the development of atherosclerosis.[55]

ROLE OF THERAPY IN SUBCLINICAL HYPOTHYROIDISM

There has been conflicting results regarding the effect of L thyroxine substitution therapy in reversing the lipid abnormalities in patients with subclinical hypothyroidism.[56]

Few studies have found that L thyroxine therapy in SH reduced the total cholesterol levels by 15mg/dl irrespective of the pretreatment levels.[57] In contrary few studies have shown a significant decrease in HDL cholesterol by 6.8%[58] and no changes noted in other lipid parameters. Also with patients with high cholesterol (TC >240mg/dl) and TSH levels (>10µIU/ml) prior to treatment, thyroid substitution therapy brought a considerable lowering of serum total and LDL cholesterol levels.[59]

Though many studies support the beneficial role of thyroid replacement in reducing dyslipidemia and risk of CAD in overt hypothyroidism, studies concerning the treatment of subclinical hypothyroidism is still not conclusive.

Hence it is evident that thyroid substitution would play a significant beneficial role in patients with prominent thyroid dysfunction (TSH>10μIU/ml), high pretreatment cholesterol levels and in patients with smoking as an additional risk factor.

However, the beneficial effect of lowering total and LDL cholesterol level in SH patients is outweighed by thyroid substitution-induced decrease in HDL cholesterol levels. Risk of exacerbating angina or inducing cardiac arrhythmia by thyroxine therapy ensures cautious use of supplementation therapy when treating people with a previous history of angina.

In patients with dyslipidemia prevalence of SH is relatively more common. Hence ,serum TSH levels should be included in the screening of patients with high serum cholesterol levels.[60] To conclude, treatment of hypercholesterolemic patients with SH results in restoration to a new thyroid status along with the reversal of lipid abnormalities, relieves certain symptoms and prevents progression of SH to overt hypothyroidism.[61]

AUTOIMMUNE THYROID DISEASE AND LIPOPROTEIN (a)

In recent studies, increased levels of lipoprotein (a) was found in euthyroid males and females with evidence of auto immune thyroid disease (increased titers of TPO and/or Thyroglobulin antibodies).[62]

However in another study, which compared the levels of lipoprotein (a) in euthyroid patients with positive thyroid auto antibodies with age and sex matched controls showing no evidence of thyroid auto immunity, the results showed no significant difference in lipid profiles including lipoprotein (a) between the two groups.[63]In the above mentioned study, apolipoprotein (a) which is known to influence Lp(a), chronic renal failure were also taken into account.

Hence the presence of auto immune thyroid disorders does not have a significant role in reversing the lipid abnormalities in patients with subclinical hypothyroidism.[64]

EVALUATION

Since hypothyroidism is one of the important causes for secondary dyslipidemia, it is of paramount importance to screen for thyroid dysfunction in patients presenting with dyslipidemia and also in patients who show an unexpected improvement or worsening of the lipid profile.

MATERIALS AND METHODS

MATERIALS AND METHODS

The study was conducted at Govt. Royapettah Hospital, Chennai between April 2014 to September 2014.

The study was performed after getting written consent from all the atients chosen for the study. Clearance was obtained from ethical committee of Govt. Kilpauk College and Hospital, Chennai.

STUDY DESIGN AND PATIENT SELECTION

This is a cross sectional, case control study in which 85 patients presenting with acute ischemic stroke are taken as cases and 85 people not suffering from stroke were selected as controls matched for age, sex and risk factors.

Inclusion Criteria:

1. patients with acute ischemic stroke
2. no previous H/O thyroid abnormality
3. no H/O any chronic drug intake known to interfere with thyroid function.

Exclusion criteria:

1. Patients with previous H/O thyroid dysfunction.
2. Cardiac dysfunction leading to embolic stroke.
3. No e/o TIA, SAH, intraparenchymal hemorrhage or mass lesion on radiographic imaging of brain.

4. Severe renal function impairment.
5. Severe liver function impairment.
6. Patients taking drugs known to interfere with thyroid function.

METHODOLOGY

A total no. of 85 patients presenting with acute ischemic stroke from both sexes (51 Males & 34 Females) with age range from 45 to 80 years were selected as cases, diagnosis confirmed by CT brain and thyroid profile (free T_3, T_4, TSH) measured in these patients.

A total no. of 85 controls (not suffering from stroke) matched for age, sex and risk factors were selected from outpatient department, Govt. Royapettah Hospital.

Patients and controls taking drugs that interfered with thyroid function were excluded from the study.

MATERIALS

Thyroid function was tested by quantitative measurements of free triiodothyronine (T_3), free Thyroxine (T_4) and Thyroid Stimulating hormone (TSH) using Chemiluinescent Micro particle Immune Assay (CMIA) technique. Under aseptic precautions, using a sterile syringe, 2ml of venous blood was withdrawn from a peripheral vein for estimating thyroid profile.

Range of Expected Values:

Free T_3 – 1.71-3.70 pg/ml

Free T_4- 0.89- 1.76 ng/dl

TSH- 0.35- 5.50 µIU/ml

So patients, with normal T_3, T_4 levels and elevated TSH levels (< 10 µIU/ml) were diagnosed to have subclinical hypothyroidism. Normal TSH levels (0.35-5.50 µIU/ml).

STATISTICAL ANALYSIS:

Data was entered in Windows Excel format, data analysis was carried out using statistical package of SPSS 15 for determination of statistical significance among different variables. Co-relation was assessed using chi-square test.

A p value of less than 0.05 was considered as significant.

RESULTS

RESULTS AND OBSERVATIONS

DISTRIBUTION OF AGE AMONG CASES

	Observed N	Expected N	Residual	P Value
<= 50	5	21.3	-16.3	
51-60	18	21.3	-3.3	0.000
61-70	35	21.3	13.8	
71-80	27	21.3	5.8	
Total	85			

Table 3: **Distribution Of Age Among Cases**

In the study, 62 were above 60 years and 23 people below 60 years. The frequency of ischemic stroke was more in the age group > 60 years 6(73%) compared with age group <60 years. The p value of the study which is <0.05 is significant.

The mean age of the patients was (65.86 ± 7.72 SD) years and for control (65.64 ± 6.74 SD) years.

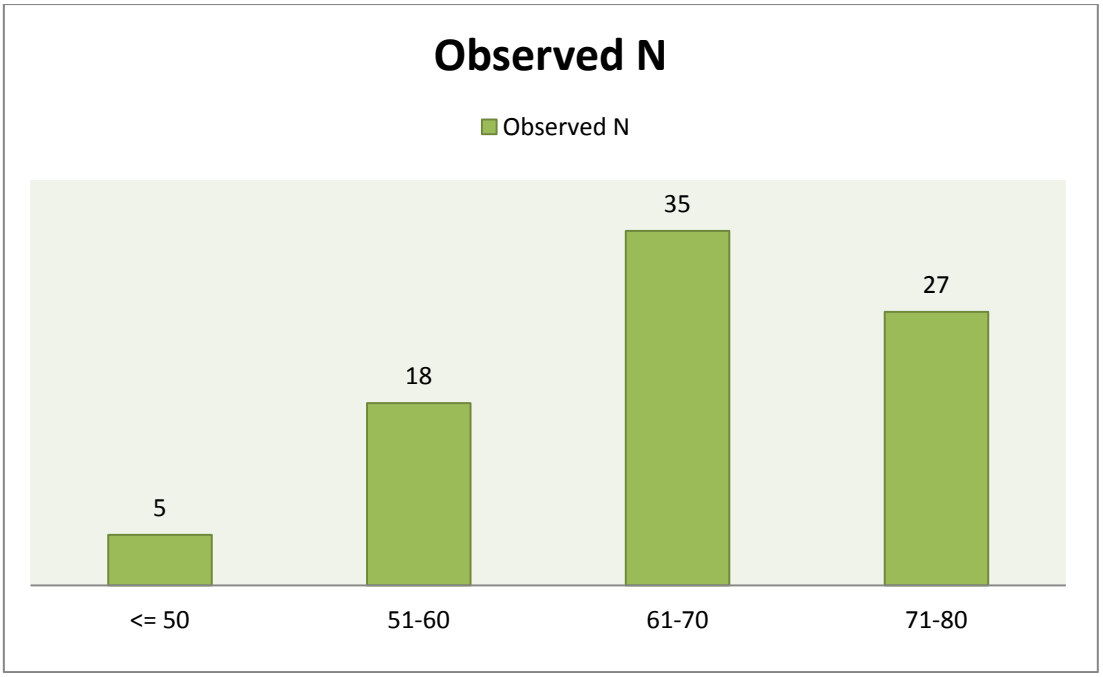

Figure 16: Distribution Of Age Among Cases

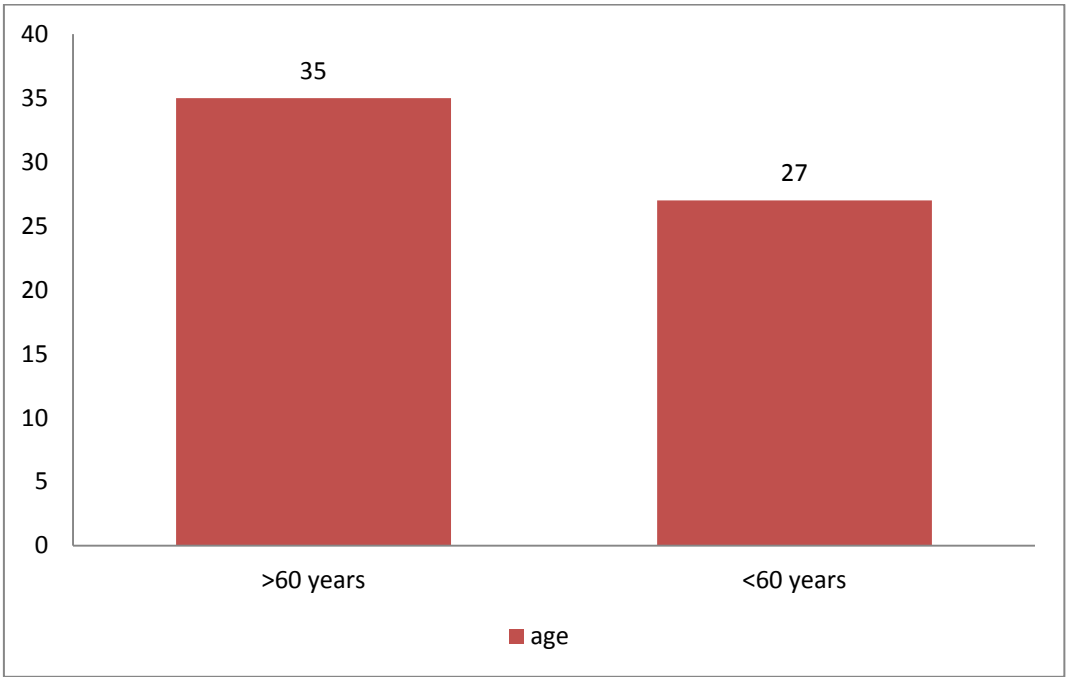

Figure 17: Distribution Of Age Among Cases

AGE DISTRIBUTION AMONG CASES AND CONTROLS

			Diagnosis		Total	P value
			Cases	Control		
Age in years	<= 50	Count	5	1	6	
		% within Age in years	83.30%	16.70%	100.00%	
		% within Diagnosis	5.90%	1.20%	3.50%	
	51-60	Count	18	16	34	
		% within Age in years	52.90%	47.10%	100.00%	
		% within Diagnosis	21.20%	18.80%	20.00%	
	61-70	Count	35	46	81	
		% within Age in years	43.20%	56.80%	100.00%	
		% within Diagnosis	41.20%	54.10%	47.60%	
	71-80	Count	27	22	49	0.188
		% within Age in years	55.10%	44.90%	100.00%	
		% within Diagnosis	31.80%	25.90%	28.80%	
Total		Count	85	85	170	
		% within Age in years	50.00%	50.00%	100.00%	
		% within Diagnosis	100.00%	100.00%	100.00%	

Table 4: **Distribution Of Age Among Cases and Controls**

The age distribution among cases and controls was equal with a p value of 0.188 which is not statistically significant.

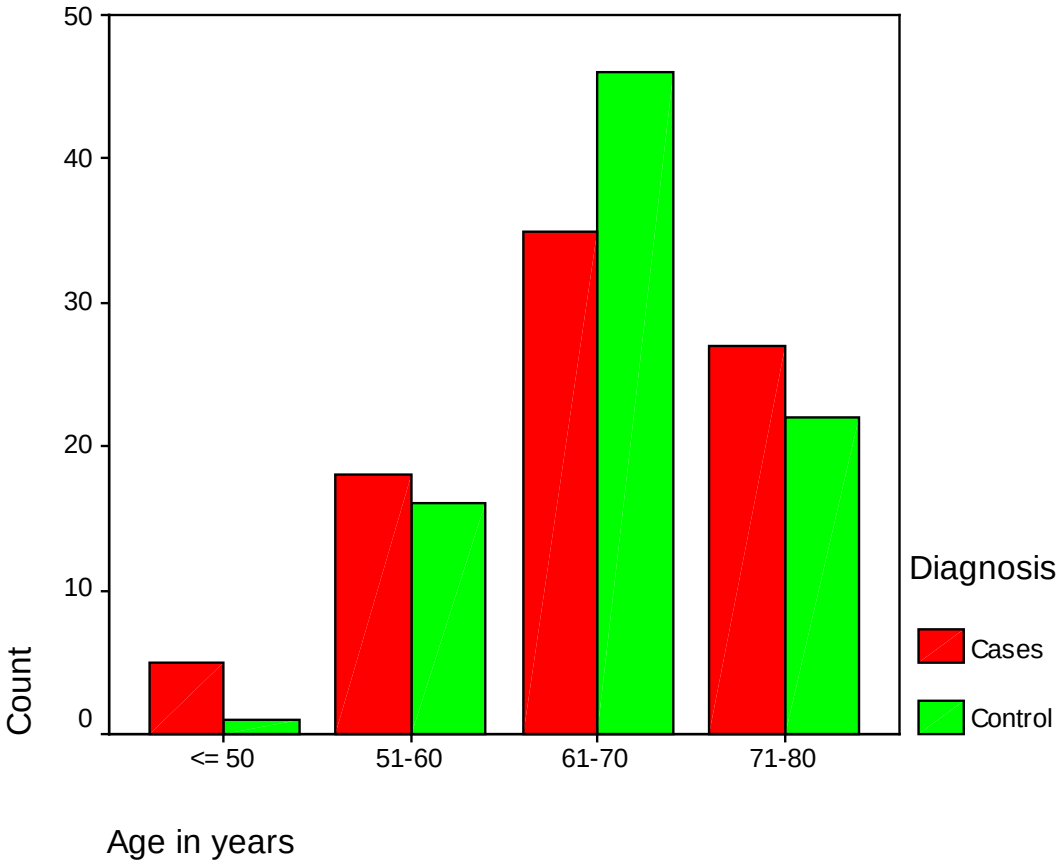

Figure 18: Age Distribution Between Case And Control Groups

GENDER DISTRIBUTION BETWEEN CASES AND CONTROLS

			Diagnosis		Total	P Value
			Cases	Control		
	Male	Count	51	51	102	1.000
		% within Sex	50.00%	50.00%	100.00%	
		% within Diagnosis	60.00%	60.00%	60.00%	
	Female	Count	34	34	68	
		% within Sex	50.00%	50.00%	100.00%	
		% within Diagnosis	40.00%	40.00%	40.00%	
Total		Count	85	85	170	
		% within Sex	50.00%	50.00%	100.00%	
		% within Diagnosis	100.00%	100.00%	100.00%	

Table 5: Gender Distribution Between Cases And Controls

In this study, the frequency of ischemic stroke was found to be higher in males (51) than females (34) but there was no correlation between gender distribution among cases and controls with a p value of 1.000 which showed no statistical significance.

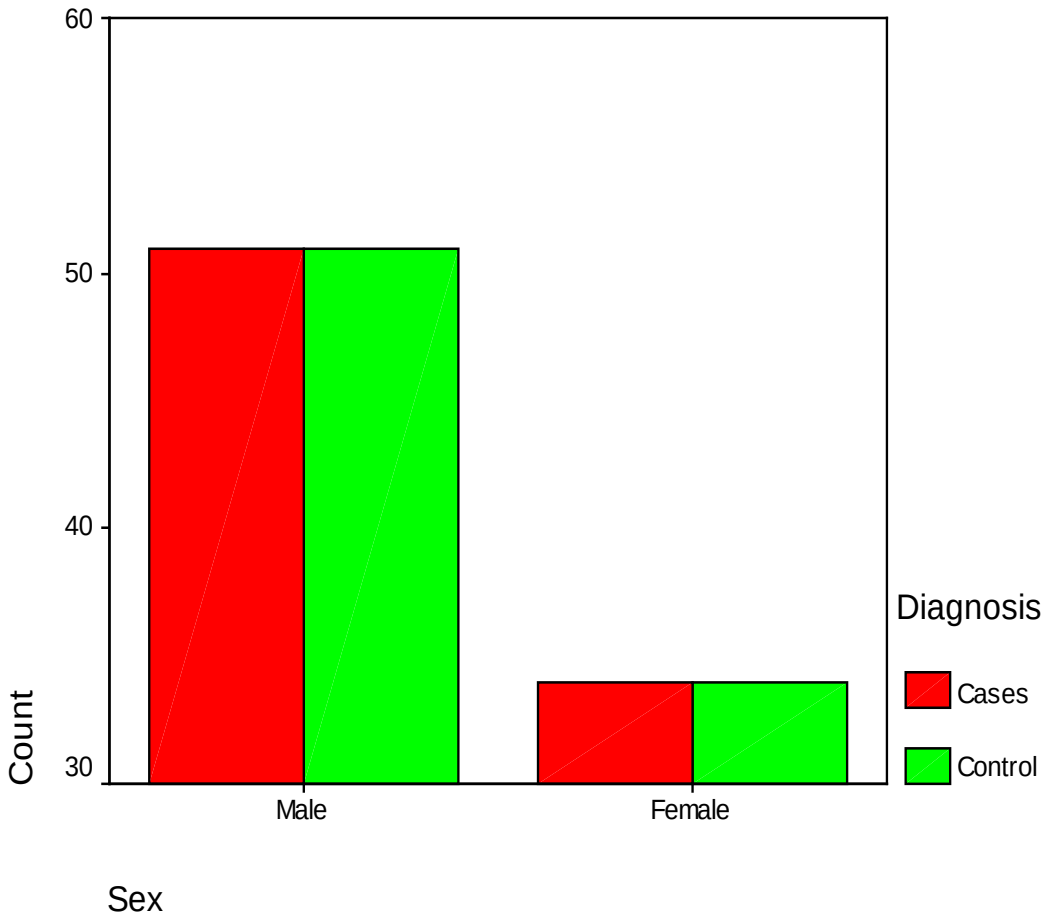

Figure 19: Gender distribution between case and control groups

In this study, the frequency of ischemic stroke was found to be higher in males (51) than females (34) but there was no correlation between gender distribution among cases and controls with a p value of 1.000 which showed no statistical significance.

RISK FACTOR DISTRIBUTION BETWEEN CASES AND CONTROLS

			Diagnosis		Total	P Value
			Cases	Control		
Past History	Nil	Count	34	34	68	1.000
		% within Past History	50.0%	50.0%	100.0%	
		% within Diagnosis	40.0%	40.0%	40.0%	
	DM	Count	20	20	40	
		% within Past History	50.0%	50.0%	100.0%	
		% within Diagnosis	23.5%	23.5%	23.5%	
	HT	Count	20	20	40	
		% within Past History	50.0%	50.0%	100.0%	
		% within Diagnosis	23.5%	23.5%	23.5%	
	Both	Count	11	11	22	
		% within Past History	50.0%	50.0%	100.0%	
		% within Diagnosis	12.9%	12.9%	12.9%	
Total		Count	85	85	170	
		% within Past History	50.0%	50.0%	100.0%	
		% within Diagnosis	100.0%	100.0%	100.0%	

Table 6: Risk Factor Distribution Between Cases And Controls

The frequency of risk factors i.e. HT, DM or both was found to be equally distributed between cases and controls in the study with a p value of 1.000 which showed no statistical significance.

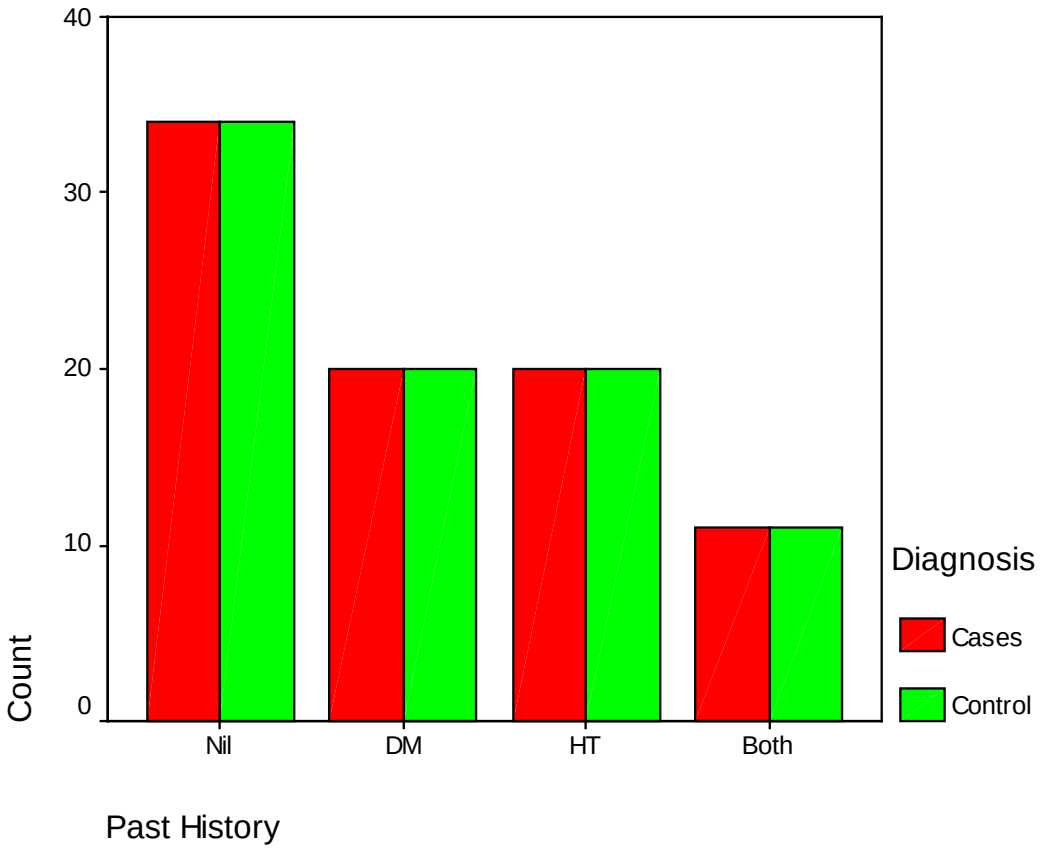

Figure 20: Risk Factor distribution between case and control groups

DISTRIBUTION OF SMOKING/ALCOHOLISM AMONG CASES AND CONTROLS

			Diagnosis		Total	P Value
			Cases	Control		
Smoker/ Alcoholic	Yes	Count	29	29	58	1.000
		% within Smoker /Alcoholic	50.0%	50.0%	100.0%	
		% within Diagnosis	34.1%	34.1%	34.1%	
	No	Count	56	56	112	
		% within Smoker/ Alcoholic	50.0%	50.0%	100.0%	
		% within Diagnosis	65.9%	65.9%	65.9%	
Total		Count	85	85	170	
		% within Smoker/ Alcoholic	50.0%	50.0%	100.0%	
		% within Diagnosis	100.0%	100.0%	100.0%	

Table 7: Distribution Of Smoking/Alcoholism Among Cases And Controls

The frequency of smoking / alcoholism was found to be equally distributed between cases and controls in the study with a p value of 1.000 which showed no statistical significance.

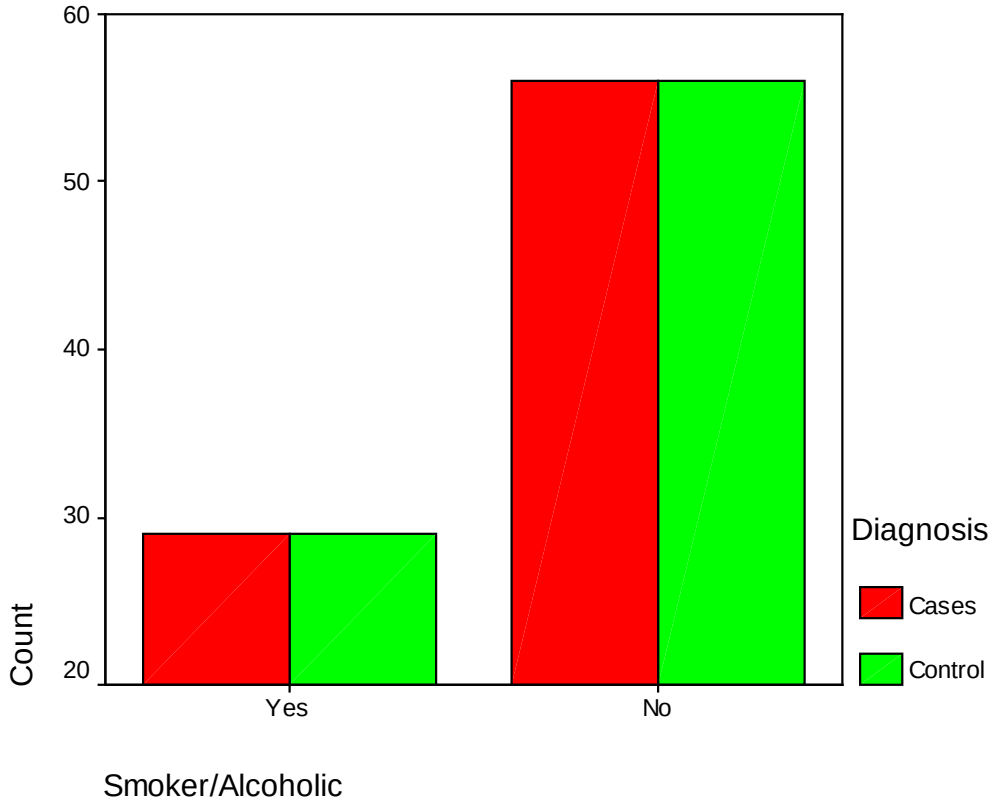

Figure 19: Distribution Of Smoking/Alcoholism Among Cases And Controls

The frequency of smoking / alcoholism was found to be equally distributed between cases and controls in the study with a p value of 1.000 which showed no statistical significance.

DISTRIBUTION OF RT/LT MCA INFARCT AMONG CASES AND CONTROLS

			Diagnosis		Total	P Value
			Cases	Control		
CNS	Left Hemiplegia	Count	60	0	60	0.000
		% within CNS	100.0%	.0%	100.0%	
		% within Diagnosis	70.6%	.0%	35.3%	
	Right Hemiplegia	Count	25	0	25	
		% within CNS	100.0%	.0%	100.0%	
		% within Diagnosis	29.4%	.0%	14.7%	
	NFND	Count	0	85	85	
		% within CNS	.0%	100.0%	100.0%	
		% within Diagnosis	.0%	100.0%	50.0%	
Total		Count	85	85	170	
		% within CNS	50.0%	50.0%	100.0%	
		% within Diagnosis	100.0%	100.0%	100.0%	

Table 8: Distribution Of Rt/Lt Mca Infarct Among Cases And Controls

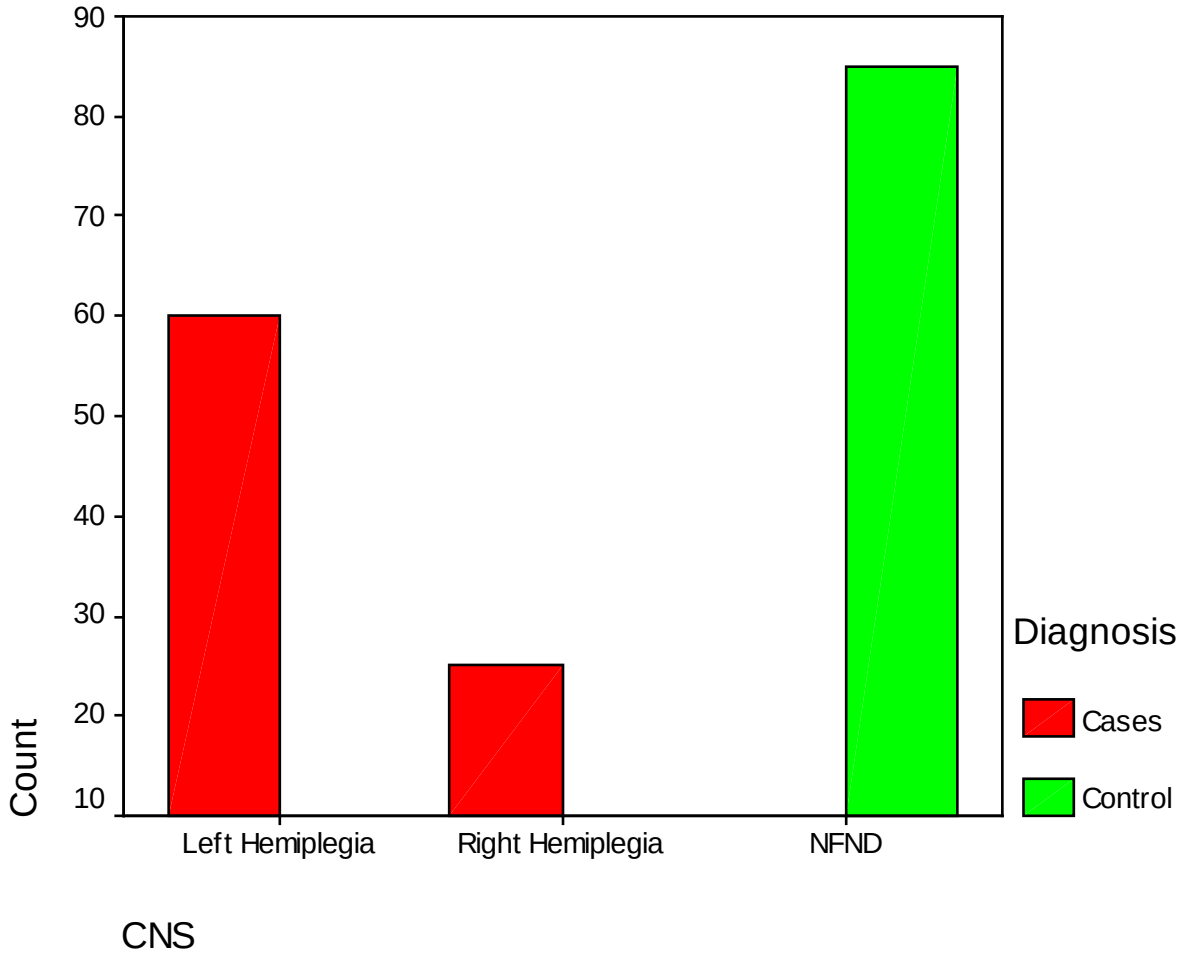

Figure 20: Distribution Of Rt/Lt Mca Infarct Among Cases And Controls

The distribution of rt MCA infarct was more common than lt MCA infarct among cases with a p value of 0.000 which is significant.

COMPARISON OF RENAL AND LIVER FUNCTION TESTS AMONG CASES AND CONTROLS

	Diagnosis	N	Mean	Std. Deviation	Std. Error Mean	P Value
Serum Urea	Cases	85	30.89	4.816	.522	>0.05
	Control	85	31.42	4.910	.533	
Serum creatinine	Cases	85	.787	.0949	.0103	
	Control	85	.791	.0908	.0098	
Serum Total Protein	Cases	85	6.761	.2875	.0312	
	Control	85	6.776	.2918	.0317	
Serum Albumin	Cases	85	4.256	.2233	.0242	
	Control	85	4.269	.2361	.0256	

Table 9: Comparison Of Renal And Liver Function Tests Among Cases And Controls

The mean serum urea in cases was 30.89 and in controls was 31.42 with a p value of 0.479 which is statistically not significant.

The mean creatinine in cases was 0.787 and in controls was 0.908 with a p value of 0.805 which is statistically not significant.

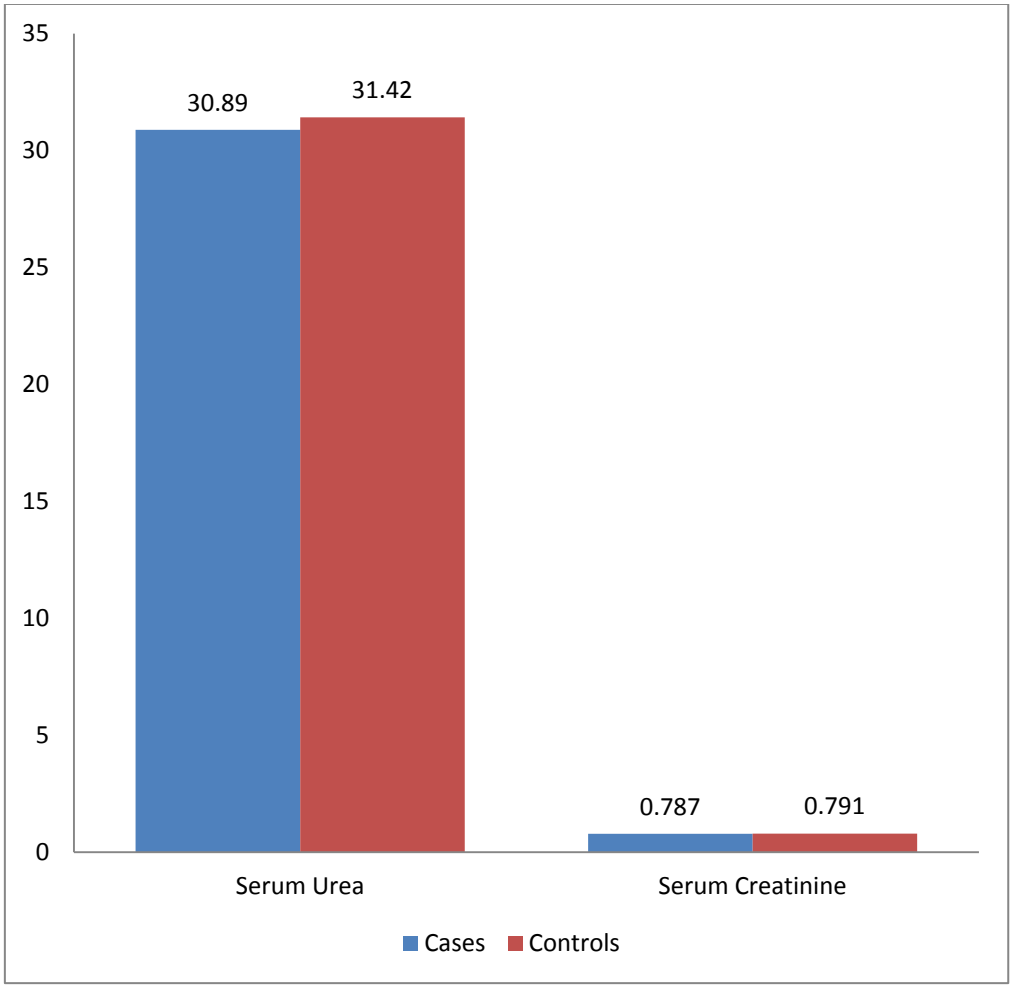

Figure 21: Comparison Of Renal Function Tests Among Cases And Controls

The mean total protein value in cases was 6.761 and in controls was 6.776 with a p value of 0.731 which is statistically not significant.

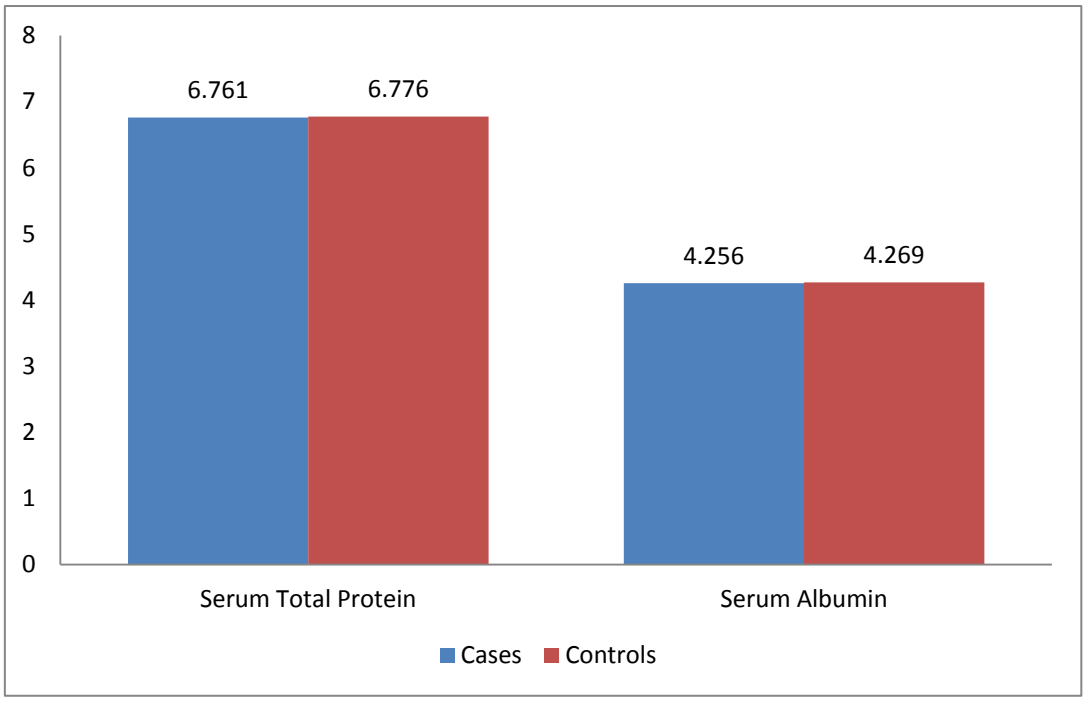

Figure 22: Comparison of Liver Function Tests Among Cases and Controls

The mean serum albumin value in cases was 4.256 and in controls was 4.269 with a p value of 0.714 which is statistically not significant.

COMPARISON OF SERUM TRIGLYCERIDE LEVELS AMONG CASES AND CONTROLS

	Diagnosis	N	Mean	Std. Deviation	Std. Error Mean	P Value
Serum Triglyceride (mg/dl)	Cases	85	133.92	16.810	1.823	0.761
	Control	85	134.71	16.896	1.833	

Table 10: Comparison Of Serum Triglyceride Levels Among Cases And Controls

The mean triglyceride level in cases was 133.92 and in controls was 34.71 and there was no significant difference in serum triglyceride levels between cases and controls with a p value of 0.761 that is not statistically significant.

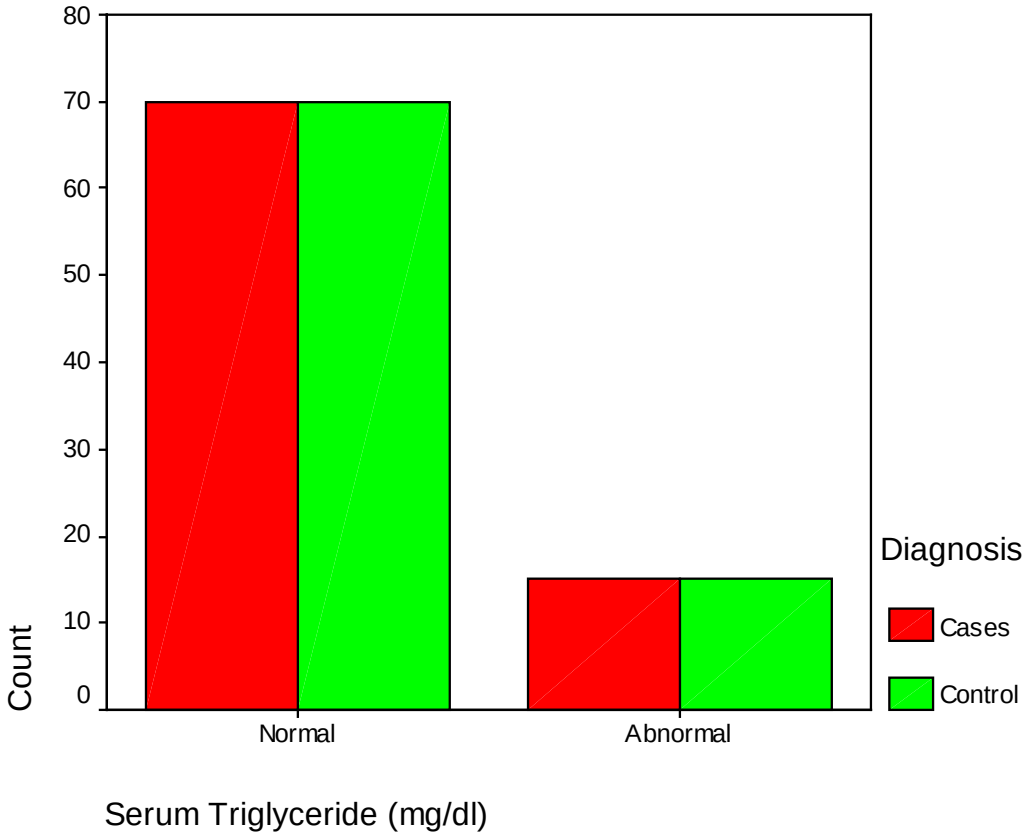

Figure 23: Serum Triglyceride distribution between case and control groups

The mean triglyceride level in cases was 133.92 and in controls was 34.71 and there was no significant difference in serum triglyceride levels between cases and controls with a p value of 0.761 that is not statistically significant.

COMPARISON OF BLOOD SUGAR VALUES AMONG CASES AND CONTROLS

	Diagnosis	N	Mean	Std. Deviation	Std. Error Mean	P Value
Random Blood Sugar (mgs%)	Cases	85	115.98	25.429	2.758	0.953
	Control	85	116.21	26.015	2.822	

Table 11: Comparison Of Blood Sugar Values Among Cases And Controls

The mean random blood sugar value in cases was 115.98 and 116.21 in controls and with a p value of 0.953 which also shows no statistical significance.

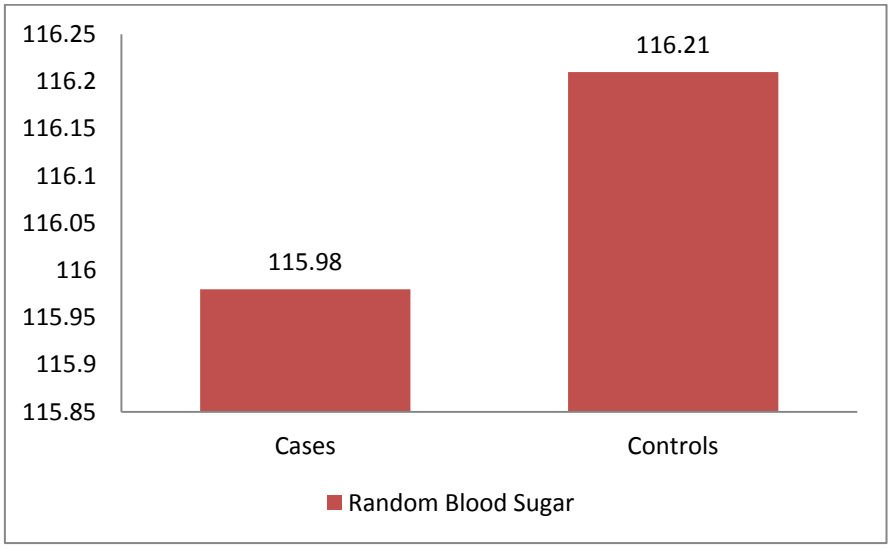

Figure 24: Comparison of Blood Sugar Values Among Cases And Controls

COMPARISON OF BLOOD PRESSURE MEASUREMENTS AMONG CASES AND CONTROLS

	Diagnosis	N	Mean	Std. Deviation	Std. Error Mean	P Value
SBP	Cases	85	165.46	10.403	1.128	
	Control	85	131.61	18.505	2.007	
DBP	Cases	85	99.98	5.778	.627	.000
	Control	85	82.94	6.828	.741	

Table 12 : Comparison Of Blood Pressure Measurements Among Cases And Controls

The mean systolic blood pressure in cases was 165.46 and in controls was 131.61 with a p value of 0.000 which is statistically highly significant.

The mean diastolic blood pressure in cases was 99.98 and in controls was 82.94 with a p value of 0.000 which is statistically highly significant.

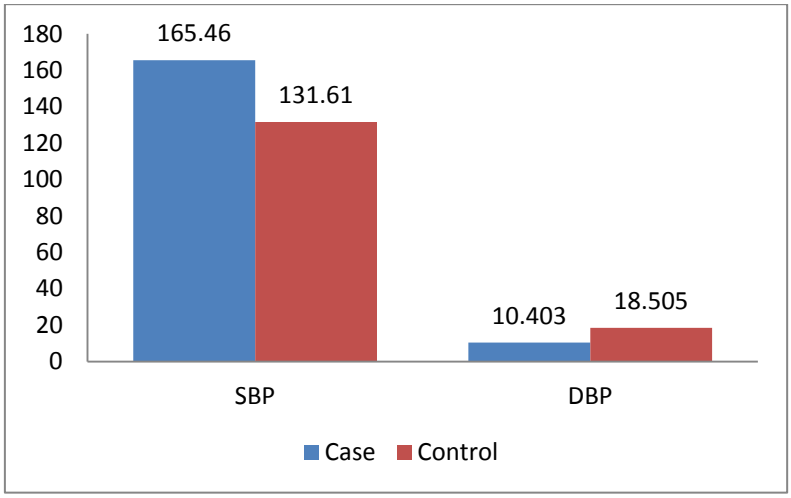

Figure 25: Comparison of Blood Pressure Measurements Among Cases And Controls

COMPARISON OF DIASTOLIC BLOOD PRESSURE AMONG EUTHYROID AND HYPOTHYROID PATIENTS

	TSH	N	Mean	Std. Deviation	Std. Error Mean	P VALUE
DBP	Normal	78	99.62	5.730	.649	0.048
	Abnormal	7	104.00	5.033	1.902	

Table 13 : Comparison of diastolic blood pressure among Euthyroid and hypothyroid patients

In the study, among cases 78 people with normal TSH values had a mean DBP of 99.62 and 7 with elevated TSH levels had a mean DBP of 104.00 which is significantly higher with a p value of 0.048 which is statistically significant.

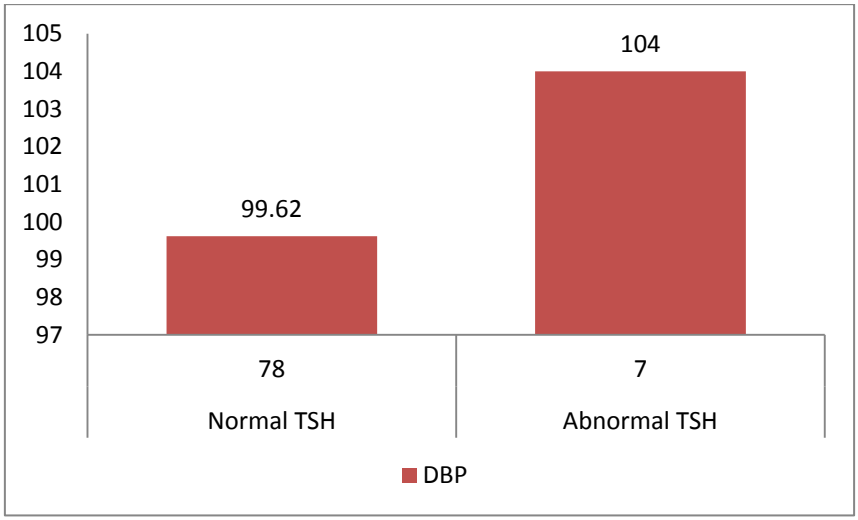

Figure 26: Comparison of diastolic blood pressure among Euthyroid and hypothyroid patients

COMPARISON OF SERUM TOTAL CHOLESTEROL BETWEEN CASES AND CONTROLS

			Diagnosis		Total	P value
			Cases	Control		
Serum Total Cholesterol	Normal	Count	70	81	151	
		% within Serum Total Cholesterol	46.4%	53.6%	100.0%	
		% within Diagnosis	82.4%	95.3%	88.8%	
	Abnormal	Count	15	4	19	0.007
		% within Serum Total Cholesterol	78.9%	21.1%	100.0%	
		% within Diagnosis	17.6%	4.7%	11.2%	
Total		Count	85	85	170	
		% within Serum Total Cholesterol	50.0%	50.0%	100.0%	
		% within Diagnosis	100.0%	100.0%	100.0%	

Table 14 : Comparison Of Serum Total Cholesterol Between Cases And Controls

In the study, among cases 70 had high serum total cholesterol and 15 had elevated serum total cholesterol and among controls 81 had had high serum total cholesterol and 4 had elevated serum total cholesterol. The mean serum total cholesterol in cases was significantly higher than in controls but the p value is 0.007 which is not statistically significant.

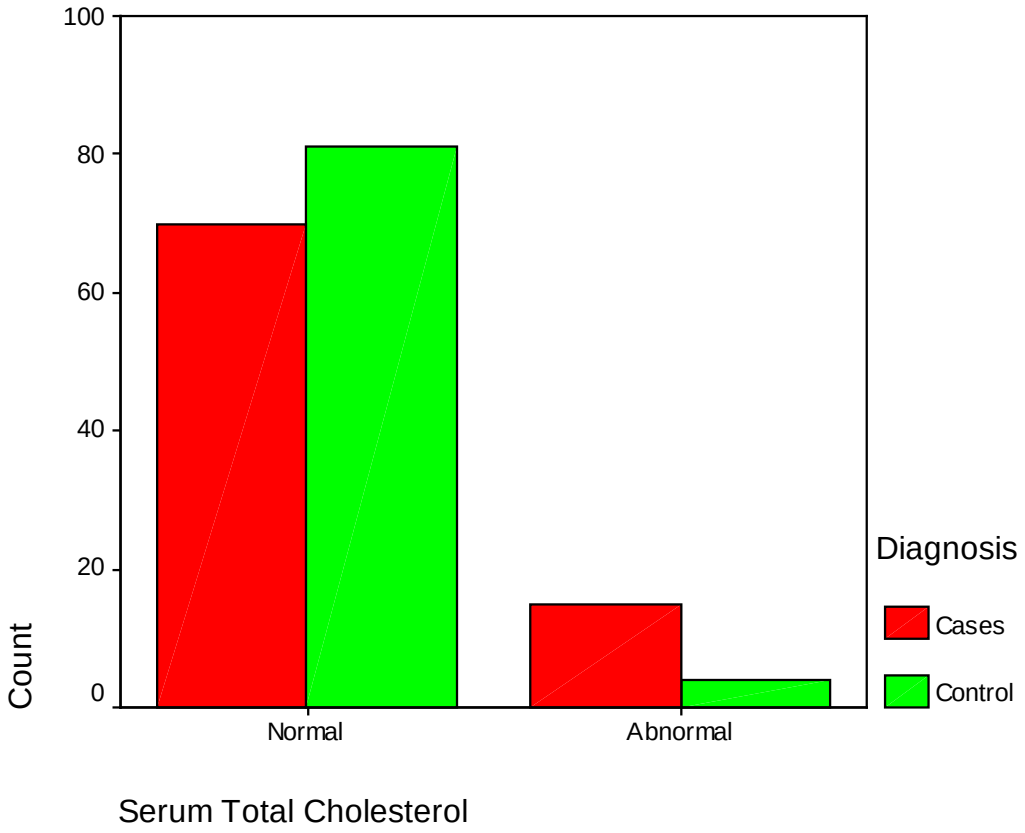

Figure 27: Comparison Of Serum Total Cholesterol Between Cases And Controls

COMPARISON OF SERUM CHOLESTEROL IN EUTHYROID PATIENTS AMONG CASES AND CONTROLS

TSH				Diagnosis		Total	P Value
				Cases	Control		
Normal	Serum Total Cholesterol	Normal	Count	69	81	150	
			% within Serum Total Cholesterol	46.0%	54.0%	100.0%	
			% within Diagnosis	88.5%	95.3%	92.0%	
		Abnormal	Count	9	4	13	
			% within Serum Total Cholesterol	69.2%	30.8%	100.0%	0.108
			% within Diagnosis	11.5%	4.7%	8.0%	
	Total		Count	78	85	163	
			% within Serum Total Cholesterol	47.9%	52.1%	100.0%	
			% within Diagnosis	100.0%	100.0%	100.0%	
Abnormal	Serum Total Cholesterol	Normal	Count	1		1	
			% within Serum Total Cholesterol	100.0%		100.0%	
			% within Diagnosis	14.3%		14.3%	

		Abnormal	Count	6		6	
			% within Serum Total Cholesterol	100.0%		100.0%	<0.001
			% within Diagnosis	85.7%		85.7%	
	Total		Count	7		7	
			% within Serum Total Cholesterol	100.0%		100.0%	
			% within Diagnosis	100.0%		100.0%	

Table 15 : Comparison Of Serum Cholesterol In Euthyroid Patients Among Cases And Controls

In the study, among patients with normal TSH levels, 69 of cases and 81 of controls had normal serum total cholesterol while 9 of cases and 4 of controls had elevated serum total cholesterol.

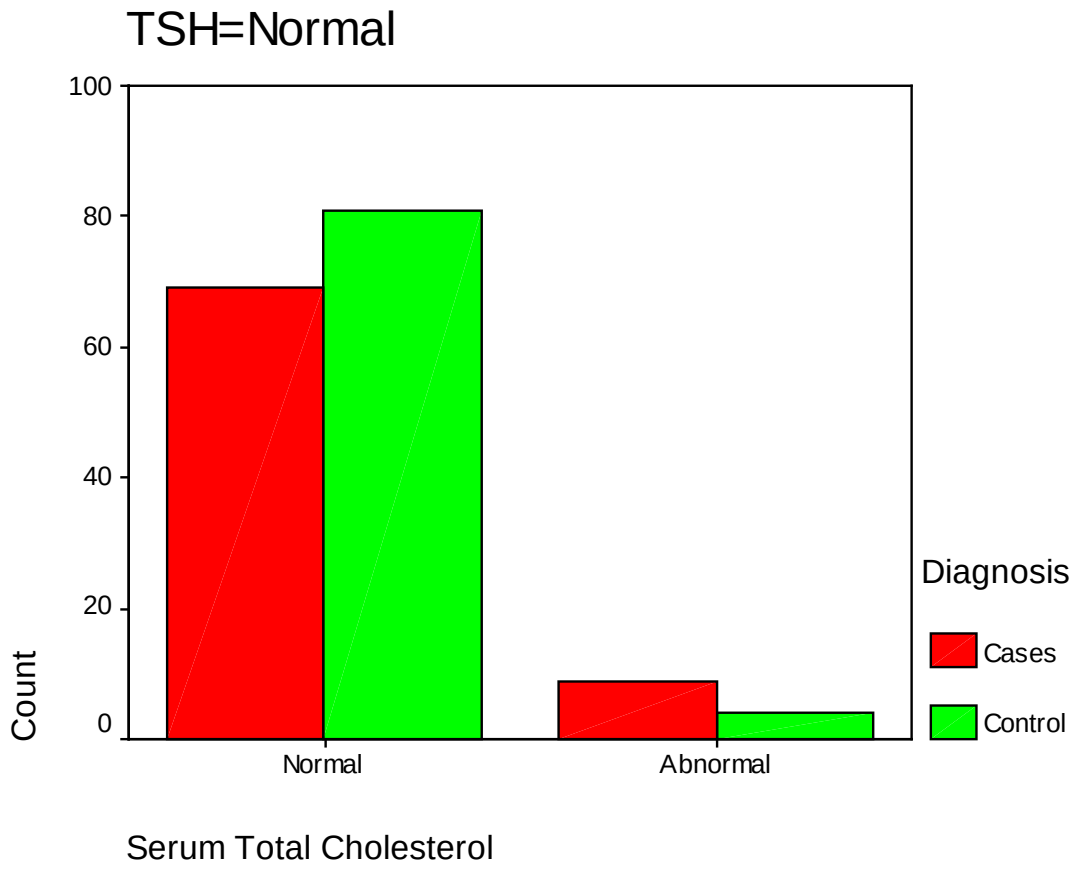

Figure 28: Comparison Of Serum Cholesterol In Euthyroid Patients Among Cases

The serum total cholesterol among cases and controls with an euthyroid pattern was found to have a p value of 0.108 which is not statistically significant.

DISTRIBUTION OF HYPOTHYROID PATIENTS ACCORDING TO SERUM CHOLESTEROL LEVELS

	Elevated TSH cases	Mean	P Value
Normal Serum Cholesterol	1	14.3	< 0.001
Abnormal Serum Cholesterol	6	85.7	

Table 16 : Distribution Of Hypothyroid Patients According To Serum Cholesterol Levels

In 7 patients with hypothyroidism, 6 patients had elevated serum cholesterol with a mean value of 85.7 compared to 1 patient who had normal cholesterol value with a mean of 14.3 which is statistically significant with a p value of <0.001.

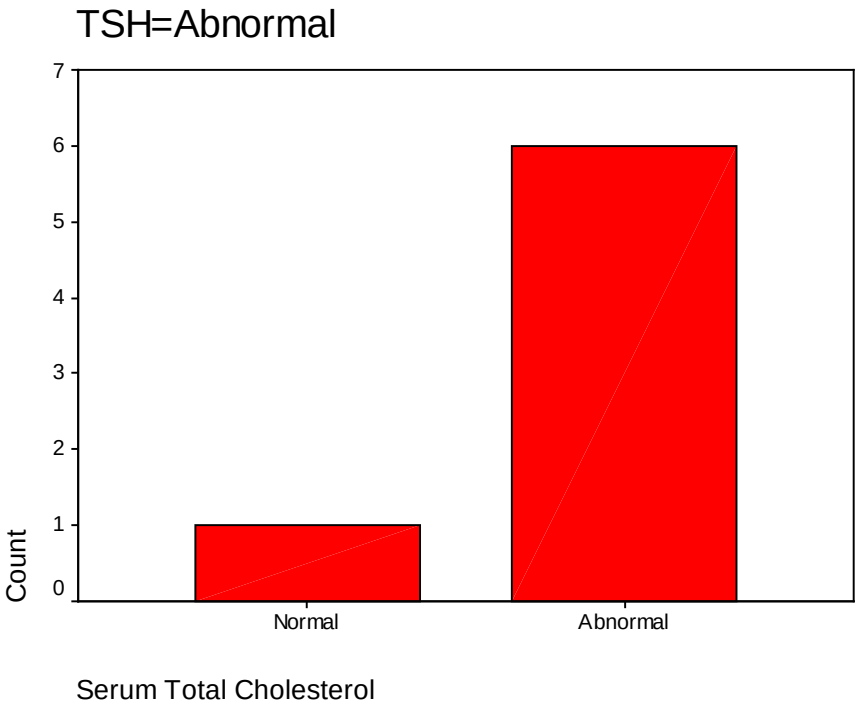

Figure 29: Distribution Of Hypothyroid Patients According To Serum Cholesterol Levels

In 7 patients with hypothyroidism, 6 patients had elevated serum cholesterol with a mean value of 85.7 compared to 1 patient who had normal cholesterol value with a mean of 14.3 which is statistically significant with a p value of <0.001.

COMPARISON OF FREE TRIIODOTHYRONINE LEVELS AMONG CASES AND CONTROLS

			Diagnosis		Total	P Value
			Cases	Control		
T3	Normal	Count	76	73	149	0.484
		% within T3	51.0%	49.0%	100.0%	
		% within Diagnosis	89.4%	85.9%	87.6%	
	Abnormal	Count	9	12	21	
		% within T3	42.9%	57.1%	100.0%	
		% within Diagnosis	10.6%	14.1%	12.4%	
Total		Count	85	85	170	
		% within T3	50.0%	50.0%	100.0%	
		% within Diagnosis	100.0%	100.0%	100.0%	

Table 17 : Comparison Of Free Triiodothyronine Levels Among Cases And Controls

In the study, among cases 76 had normal free T_3 levels and 9 had low free T_3 levels. Among controls 73 had normal free T_3 levels and 12 had low free T_3 levels.The free T_3levels variation was equal in both cases and controls with a p value of 0.484 which is statistically not significant.

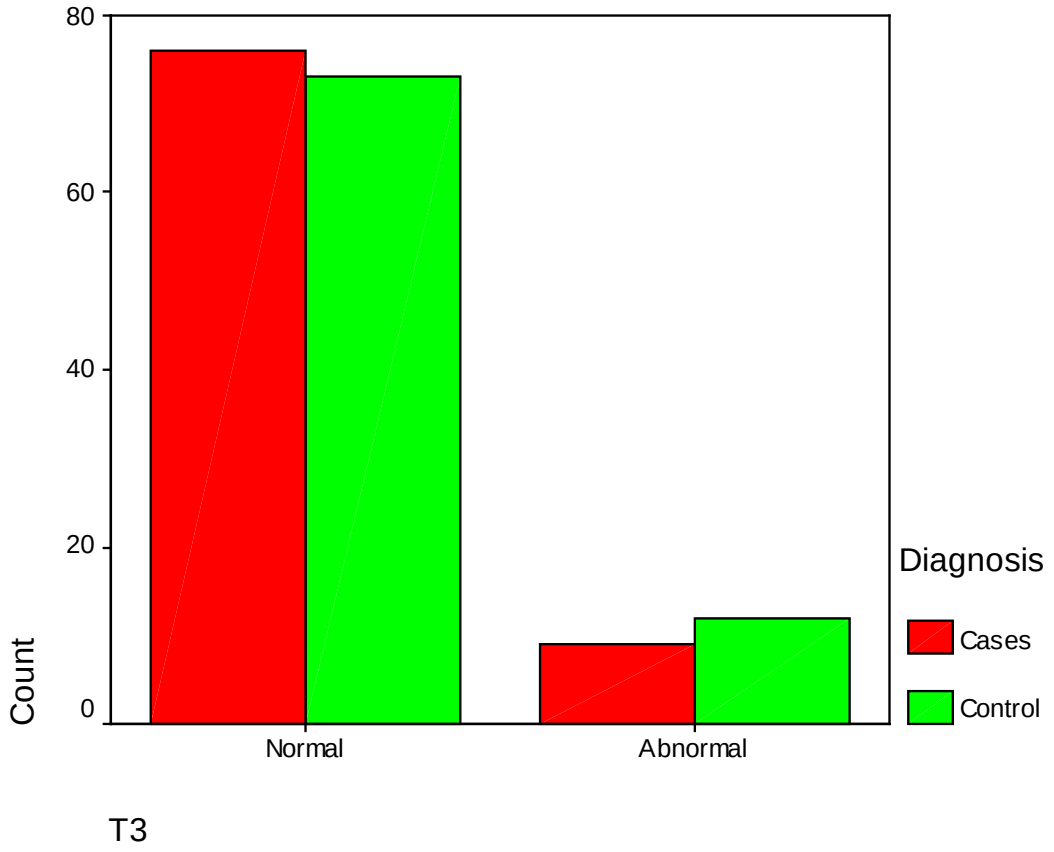

Figure 30: Comparison Of Free Triiodothyronine Levels Among Cases And Controls

In the study, among cases 76 had normal free T_3 levels and 9 had low free T_3 levels. Among controls 73 had normal free T_3 levels and 12 had low free T_3 levels.The free T_3levels variation was equal in both cases and controls with a p value of 0.484 which is statistically not significant.

COMPARISON OF FREE T_3 LEVELS AMONG CASES AND CONTROLS

			Diagnosis		Total	P Value
			Cases	Control		
T4	Normal	Count	78	80	158	0.549
		% within T4	49.4%	50.6%	100.0%	
		% within Diagnosis	91.8%	94.1%	92.9%	
	Abnormal	Count	7	5	12	
		% within T4	58.3%	41.7%	100.0%	
		% within Diagnosis	8.2%	5.9%	7.1%	
Total		Count	85	85	170	
		% within T4	50.0%	50.0%	100.0%	
		% within Diagnosis	100.0%	100.0%	100.0%	

Table 18 : COMPARISON OF FREE T_3 LEVELS AMONG CASES AND CONTROLS

In our study among cases78 had normal freeT_4 and 7 had lowT_4 levels while in controls 80 had normal T_4 and 5 had low freeT_4 levels. The free T_4 levels variation was equal among cases and controls with a p value of 0.549 which is statistically not significant.

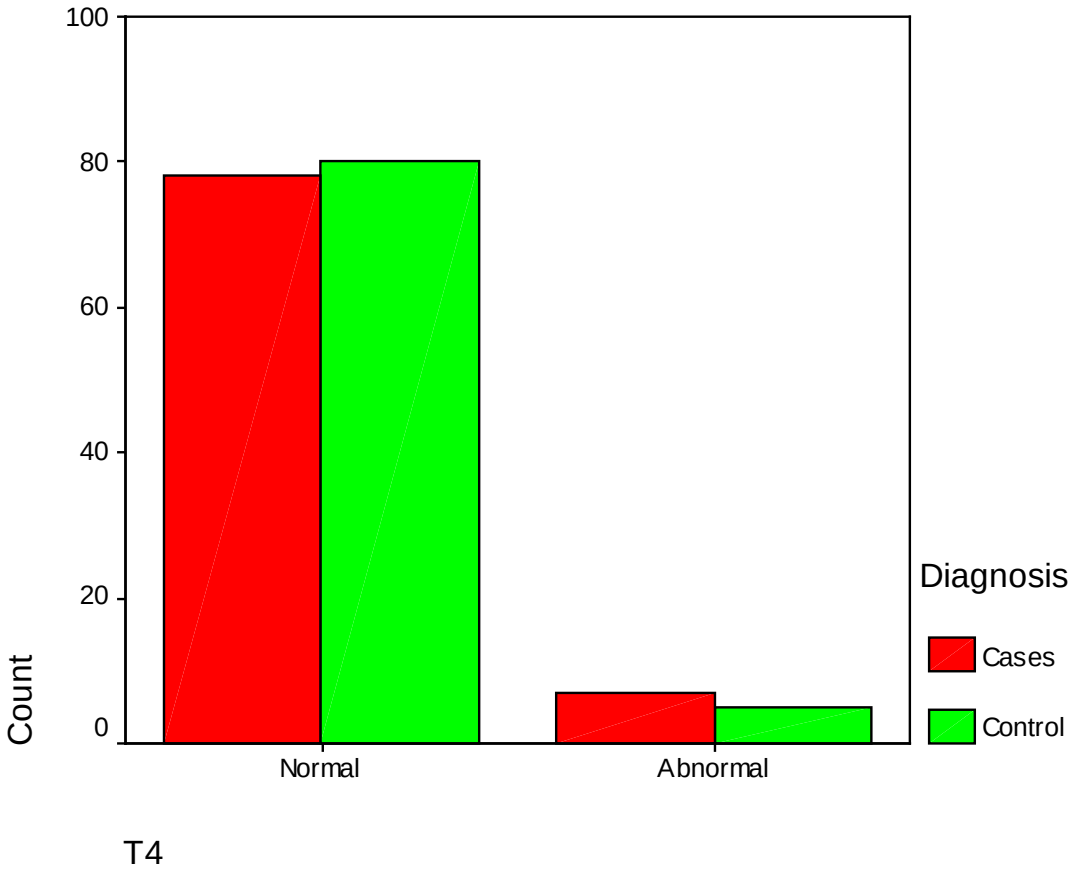

Figure 31: Comparison Of Free T_3 levels Among Cases And Controls

In our study among cases78 had normal freeT_4 and 7 had lowT_4 levels while in controls 80 had normal T_4 and 5 had low freeT_4 levels. The free T_4 levels variation was equal among cases and controls with a p value of 0.549 which is statistically not significant.

DISTRIBUTION OF SICK EUTHYROIDISM AMONG CASES AND CONTROLS.

			Diagnosis		Total	P Value
			Cases	Control		
Sick Euthyroid	Normal	Count	70	68	138	0.695
		% within Sick Euthyroid	50.7%	49.3%	100.0%	
		% within Diagnosis	82.4%	80.0%	81.2%	
	Abnormal	Count	15	17	32	
		% within Sick Euthyroid	46.9%	53.1%	100.0%	
		% within Diagnosis	17.6%	20.0%	18.8%	
Total		Count	85	85	170	
		% within Sick Euthyroid	50.0%	50.0%	100.0%	
		% within Diagnosis	100.0%	100.0%	100.0%	

Table 19 : Distribution Of Sick Euthyroidism Among Cases And Controls.

In the study, among cases 70 had normal freeT_3 and free T_4 levels and 15 had low freeT_3 and free T_4 levels.among controls 68 had normal freeT_3 and free T_4 levels and 17 had low freeT_3 and free T_4 levels.

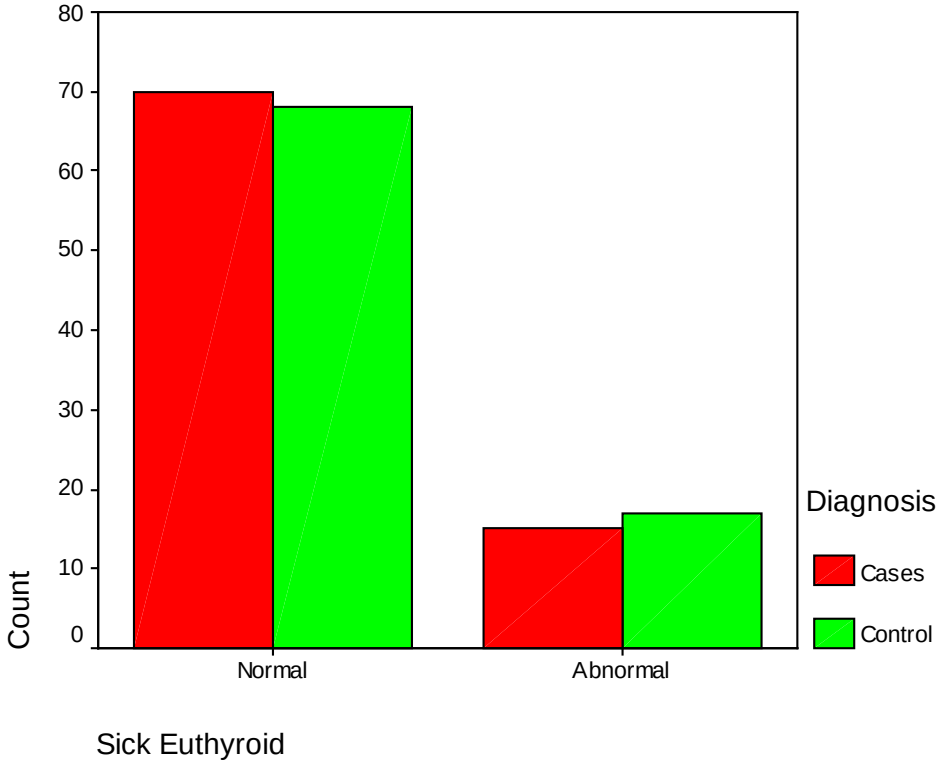

Figure 32: Distribution Of Sick Euthyroidism Among Cases And Controls.

Sick euthyroid levels was found to be equally distributed between cases and controls with a p value of 0.695 which showed no statistical significance.

DISTRIBUTION OF TSH LEVELS AMONG CASES AND CONTROLS

			Diagnosis		Total	P Value
			Cases	Control		
TSH	Normal	Count	78	85	163	0.007
		% within TSH	47.9%	52.1%	100.0%	
		% within Diagnosis	91.8%	100.0%	95.9%	
	Abnormal	Count	7	0	7	
		% within TSH	100.0%	.0%	100.0%	
		% within Diagnosis	8.2%	.0%	4.1%	
Total		Count	85	85	170	
		% within TSH	50.0%	50.0%	100.0%	
		% within Diagnosis	100.0%	100.0%	100.0%	

Table 20 : Distribution Of Tsh Levels Among Cases And Controls

In our study, out of 85 controls 78 patients had normal TSH levels and 7 patients had elevated TSH levels compared to controls in which all 85 people had normal TSH levels. The p value was <0.05 which is statistically significant.

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
For cohort Diagnosis = Cases	.479	.408	.562
N of Valid Cases	170		

In our study, out of 85 controls 78 patients had normal TSH levels and 7 patients had elevated TSH levels compared to controls in which all 85 people had normal TSH levels. The p value was <0.05 which is statistically significant.

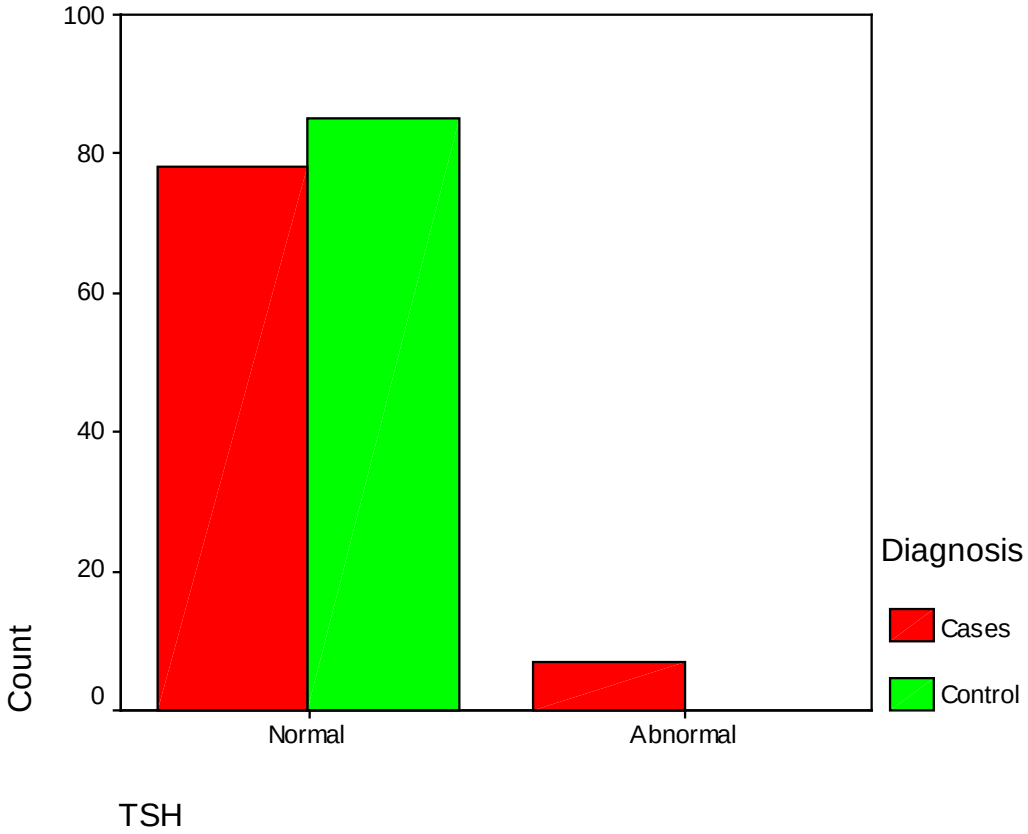

Figure 33: Distribution Of Tsh Levels Among Cases And Controls

DISCUSSION

DISCUSSION

The study is a cross sectional case control study done in Govt. Royapettah Hospital and 85 patients with acute ischemic stroke are taken as cases and 85 people not suffering from stroke acting as controls matched for age, sex and risk factors. Base line investigations and thyroid hormonal profile consisting of free T_3, T_4 and TSH was measured and the association of subclinical hypothyroidism with acute ischemic stroke was studied.

AGE

In the study, 62 were above 60 years and 23 people below 60 years. The mean age of the patients was (65.86 ± 7.72 SD) years and for control (65.64 ± 6.74 SD) years. The frequency of ischemic stroke was more in the age group > 60 years 6(73%) compared with age group <60 years

These results were consistent with brown et al[65] study who showed that patient older than 55 years had high risk of stroke ,statistically significance (p=0.001). This is because of the fact that the age is one of the most powerful independent risk factor for atherosclerosis.

GENDER

In our study, majority of patients were males (51) and females (34) with a M:F ratio of 2:1 but there was no statistical difference between males and females in cases and controls.

This is consistent with Rodica E. Petrea[66] et al study which showed no statistical difference between male and female especially in age group more than 55 years. This can be explained by hormonal changes after menopause that makes the risk of ischemic stroke equal in both sexes.

BLOOD PRESSURE

The mean systolic blood pressure in cases was higher than in controls with a p value of 0.000 and the mean diastolic blood pressure was also higher in cases than controls with a p value of 0.000.

These results were consistent with Johansan et al study[67] who showed that patient with hypertension high risk of stroke, statistically significance (p=0.001). The high blood pressure during an ischemic stroke accounts for the auto regulation and neuro protective mechanism of the cerebral vasculature to maintain cerebral perfusion.

DIABETES MELLITUS

The mean random blood sugar value in cases was 115.98 and 116.21 in controls and with a p value of 0.953 which also shows no statistical significance.

These results were inconsistent with Elizabeth Bereth Honor et al[69] study findings support the hypothesis that diabetes may confer excess risk of stroke independent of blood pressure.

These results were consistent with Ellen Air et al study[68]**,** there is no clear relationship between hyperglycemia and stroke incidence.

SERUM TRIGLYCERIDE LEVELS

The mean triglyceride level in cases was 133.92 and in controls was 134.71 and there was no significant difference in serum triglyceride levels between cases and controls with a p value of 0.761 that is not statistically significant.

These results were consistent with Akram Mohammed Al-Mahdawi et al study These results were inconsistent with Funke H[70], et al study, in which it was noticed, high serum triglyceride levels 50% (95% CI, 29% to 76%) had increased risk of fatal or nonfatal stroke.

SERUM TOTAL CHOLESTEROL

In our study, among cases 70 had high serum total cholesterol and 15 had elevated serum total cholesterol and among controls 81 had had high serum total cholesterol and 4 had elevated serum total cholesterol. There was significant difference in serum total cholesterol between cases and controls with a statistically significant p value of 0.007.

This was consistent with several other studies Yamagishi K et al[71] which showed excess risk of ischemic stroke was observed in men with serum total cholesterol levels of ≥ 6.21 mmol/L than those with the lowest category (<4.65 mmol/L).

SUBCLINICAL HYPOTHYROIDISM

In our study, out of 85 controls 78 patients had normal TSH levels and 7 patients had elevated TSH levels compared to controls in which all 85 people had normal TSH levels. patients with subclinical hypothyroidism has high association with ischemic stroke which is statistically significant with a p value of 0.007.

This was consistent with Remmel KS et al studies[72] which revealed that 12% of patients with AIS or TIA had hypothyroidism.

This was consistent with A. Squizzato et al study[73] which reveals that hypothyroidism as a possible risk factor for atherothrombotic stroke.

This is explained by the following probable mechanisms.

1. Hypothyroidism may lead to decrease myocardial contractility and heart rate with increase vascular resistance and hypertension particularly diastolic hypertension
2. Increase in serum and total and LDL cholesterol levels by down regulation of LDL receptors thereby altering endothelial function.
3. Reduced endothelium dependent vasodilation and impaired NO availability.
4. Alteration in the L-arginine-NO pathway leading to impaired NO availability.
5. Effects of inflammation and autoimmunity also contributes to endothelial dysfunction.

6. The direct effect of thyroid hormone, inflammatory status and altered lipid profile jointly contributes to impaired endothelium dependent vasodilation and progression of atherosclerosis leading to increased incidence of stroke.

HYPOTHYROIDISM AND DIASTOLIC BLOOD PRESSURE

In the study, among cases 78 people with normal TSH values had a mean DBP of 99.62 and 7 with elevated TSH levels had a mean DBP of 104.00 which is significantly higher with a p value of 0.048 which is statistically significant.
It is consistent with Ikuo Saito et al study[74] which states that diastolic blood pressure above 160/95 mm Hg (14.8% vs 5.5%; $p < 0.01$). These results suggest a close association between hypertension and hypothyroidism.

Through sympathetic and adrenaline activation and increased peripheral resistance leading to vessel wall (aortic) stiffness produces diastolic hypertension.

HYPOTHYROIDISM AND TOTAL SERUM CHOLESTEROL

In our study, 7 patients with hypothyroidism, 6 patients had elevated serum cholesterol with a mean value of 85.7 compared to 1 patient who had normal cholesterol value with a mean of 14.3 which is statistically significant with a p value of <0.001.

The results were consistent with the E.N Liberopoulos et al study[75] found an association between SH and aortic atherosclerosis (OR 1.7; 95% CI 1.1 - 2.6).

The results were consistent with R. P. F. Dullaart et al study[76] which showed that Cholesteryl ester transfer activity was 15% lower during hypothyroidism ($P < 0.02$) resulting in high total cholesterol levels.

Hypothyroidism causes down regulation of LDL receptors leading to decreased receptor mediated catabolism of LDL and IDL and increased serum total cholesterol levels.

OTHER PARAMETERS

Renal function tests

The mean serum urea in cases was 30.89 and in controls was 31.42 with a p value of 0.479 which is statistically not significant. The mean creatinine in cases was 0.787 and in controls was 0.908 with a p value of 0.805 which is statistically not significant.

The results were consistent with Laurent Fauchier et al study[77], which states that Renal impairment was not an independent predictor of ischemic stroke.

Liver function tests

The mean total protein value in cases was 6.761 and in controls was 6.776 with a p value of 0.731 which is statistically not significant.

The mean serum albumin value in cases was 4.256 and in controls was 4.269 with a p value of 0.714 which is statistically not significant.

Sick Euthyroid

In the study, among cases 70 had normal freeT_3 and free T_4 levels and 15 had low freeT_3 and free T_4 levels.among controls 68 had normal freeT_3 and free T_4 levels and 17 had low freeT_3 and free T_4 levels.

The results were consistent with Hershman J M et al study[78] which showed that Low concentrations of T3 or T4, ro both, in nonthyroidal illnesses may have a homeostatic signficance. Low serum concentrations of T4 correlate with poor prognosis in nonthyroidal illnesses.

CONCLUSION

CONCLUSIONS:

1. Subclinical hypothyroidism per se caused reduced endothelium dependent vasodilation and impaired NO availability.
2. Altered lipid profile was found to have a significant association with sub clinical hypothyroidism, especially total serum cholesterol and LDL cholesterol.
3. Chronic inflammation associated with auto immune thyroid disorders may play a role in causing endothelial dysfunction.
4. Subclinical hypothyroidism was found to be an independent, modifiable risk factor for stroke
5. Hence suggested emphasis on thyroid profile measurements, early diagnosis and management and its potential role as a modifiable risk factor in stroke prevention.

LIMITATIONS

LIMITATIONS OF THE STUDY:

1. The sample size was relatively small. Since the prevalence of subclinical hypothyroidism is low in the general population, a large sample size would yield a better understanding of co relation between the studied variables.
2. A systematic investigation of stroke risk, comparing hThy to non-hThy subjects, contolling for other known risk factors is needed to further elucidate this relationship.

DIAGNOSTIC AND THERAPEUTIC IMPLICATIONS

Stroke is one of the leading causes of morbidity and mortality and is also one of the major non communicable diseases having a significant impact on the socio economic and health status of the general population. Apart from the conventional risk factors, identification and treatment of modifiable risk factors can significantly reduce the incidence of stroke.

Subclinical hypothyroidism was found to be associated with altered lipid profile, endothelial dysfunction, increased peripheral resistance in vessel walls resulting in diastolic hypertension all favouring towards progression of atherosclerosis, the forerunner of stroke.

In the study conducted in our hospital, there was a significant association of subclinical hypothyroidism and acute ischemic stroke with a p value of 0.007 which was statistically significant.

Therefore, subclinical hypothyroidism may have a role in stroke prevention in the presence/absence of other risk factors. In addition to this early diagnosis and management plays a significant role in reducing dyslipidemia and its attending macrovascular complications.

So, owing to its low cost and easy availability, this could serve as a useful tool in identifying and preventing patients at risk for stroke thereby reducing the amount of health burden in the community.

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ANNEXURES

ABBREVIATIONS

Apo a	–	apolipoprotein a
Lp a	–	lipoprotein a
LDL	–	low density lipoprotein
HDL	–	high density lipoprotein
TGL	–	triglycerides
NO	–	nitric oxide
T_3	–	triiodothyronine
T_4	–	Thyroxine
TSH	–	thyroid stimulating hormone
SH	–	subclinical hypothyroidism
SBP	–	systolic blood pressure
DBP	–	diastolic blood pressure
T_g	–	thyroglobulin
TPO	–	Thyroperoxidase
NIS	–	Sodium iodide symporter
TRH	–	thyrotropin releasing hormone
CT	–	Computerised tomography
ROS	–	Reactive oxygen species
eNOS	--	Endothelial nitric oxide synthetase

PROFORMA

NAME : OCCUPATION:

AGE/SEX: ADDRESS:

Diagnosis :

Past historyand h/o anydrug intake:

Personal history:

PHYSICAL EXAMINATION:

Height Weight

Vitals :

CVS :

RS :

P/A:

CNS:

INVESTIGATIONS:

1.CompleteHemogram

2.RFT

3.LFT

4.ECG

5.ECHO

6.SERUM LIPID PROFILE.

7.THYROID PROFILE

8.CT BRAIN

Name	Age	Sex	Hemilegia	Past History	Personal History	SBP	DBP	RBS	S. Urea	S. Cr	Total Protein	serum Albumin	ECG	TGL	T. Chol.	CT Brain	F T3	F T4	TSH
Ramkumar	58	M	Y	DM/HT	NIL	160	100	132	28	0.7	6.2	4.2	NSR	126	182	Rt MCA Infarc	57.7	4.63	1.21
Sekar	62	M	N	DM/HT	NIL	140	100	120	33	0.9	6.8	4.4	NSR	128	176		104.4	4.71	0.93
Chellapan	72	M	Y	DM/HT	S/A	170	100	116	38	0.7	7.6	4.6	NSR	118	206	Rt MCA Infarc	72.4	6.71	2.12
Natesan	70	M	N	DM/HT	S/A	*146*	*90*	108	23	1.1	7.4	4	NSR	108	160		80.2	6.8	3.4
Elumalai	60	M	Y	DM/HT	S/A	160	106	150	32	0.7	6.9	4.3	NSR	142	200	Lt MCA Infarc	40.8	7.12	2.92
Jamal Bhai	62	M	N	DM/HT	S/A	140	90	146	33	0.8	6.6	4.1	NSR	140	177		69.9	5.96	2.9
Sivakumar	54	M	Y	DM/HT	NIL	180	100	127	21	0.9	7.5	4.5	NSR	162	188	Rt MCA Infarc	89.9	4.58	3.42
Ponmudy	56	M	N	DM/HT	NIL	146	88	142	32	0.7	7.7	4.3	NSR	160	172		103.3	5.66	2.11
Elumalai	55	M	Y	N	S/A	148	80	106	36	0.8	7.2	3.9	NSR	132	213	Rt MCA Infarc	57.5	5.7	0.65
Sankar	56	M	N	N	S/A	120	70	94	32	0.8	6.8	4.4	NSR	130	185		67.9	9.5	1.21
Babu	55	M	Y	N	NIL	150	100	98	40	1	6.2	4.6	NSR	142	172	Lt MCA Infarc	45.3	5.77	2.04
velan	52	M	N	N	NIL	120	80	85	36	0.7	6.8	4	NSR	141	208		92.3	8.1	2.14
Saukat Ali	55	M	Y	N	S/A	162	90	102	28	0.7	6.4	4.3	NSR	126	148	Rt MCA Infarc	98.4	7.8	2.56
Jeyabalan	55	M	N	N	S/A	110	80	92	32	0.9	6.7	4.1	NSR	108	165		72.6	5.77	0.78
Babu	49	M	Y	N	NIL	150	90	88	33	0.7	6.5	4.5	NSR	116	152	Rt MCA Infarc	57	4.44	2.69
Jeyakandhar	48	M	N	N	NIL	130	80	162	39	0.9	6.9	4.3	NSR	128	148		85	9.38	2.11
Srinivasan	75	M	Y	N	NIL	170	102	101	32	0.9	7.2	4.3	NSR	108	206	Rt MCA Infarc	80.8	5.2	7.05
Perumal	72	M	N	N	NIL	138	80	144	36	0.7	6.8	3.9	NSR	142	159		106.2	8.31	2.67
Devadas	57	M	Y	N	S/A	150	100	92	32	0.8	6.2	4.4	NSR	140	182	Lt MCA Infarc	87.7	5.7	1.4
Jayamani	58	M	N	N	S/A	110	80	96	36	0.8	6.8	4.6	NSR	162	172		78.2	4.94	2.37
varadhan	75	M	Y	N	S/A	190	104	110	32	0.7	6.4	4	NSR	160	211	Rt MCA Infarc	65.5	7.8	7.63
Jeyavel	72	M	N	N	S/A	130	70	100	26	1	6.7	4.3	NSR	132	186		49.9	9.38	0.92
ganesan	70	M	Y	N	S/A	200	106	101	42	1.2	6.5	4.1	NSR	130	180	Lt MCA Infarc	55.2	6.54	1.92
Parusuraman	71	M	N	N	S/A	120	80	94	28	0.9	6.9	4.4	NSR	142	182		39.8	5.01	1.86
Sekar	60	M	Y	N	NIL	170	90	98	32	0.7	6.8	4.6	NSR	141	172	Rt MCA Infarc	83.2	3.53	2.42
Vadivel	62	M	N	N	NIL	120	80	89	33	0.7	6.4	4	NSR	126	168		88.9	4.88	2.19
Sampath	70	M	Y	N	S/A	190	104	99	32	0.9	6.7	4.3	NSR	108	198	Rt MCA Infarc	36.9	8.6	1.42
Antony	71	M	N	N	S/A	130	80	102	36	0.7	6.5	4.1	NSR	116	180		76.5	6.56	1.48
Somasundar	70	M	Y	N	NIL	170	98	101	32	0.8	6.9	4.5	NSR	128	210	Rt MCA Infarc	48.5	7.4	2.98
Ramamurthy	74	M	N	N	NIL	110	80	93	26	0.9	7.2	4.3	NSR	132	184		59.8	5.51	2.94

Mannu	70	M	Y	N	S/A	180	90	105	36	0.7	6.8	4.3	NSR	130	190	Lt MCA Infarct	62.2	4.71	3.46
Kabali	72	M	N	N	S/A	120	70	98	28	1.1	6.2	3.9	NSR	142	168		48.3	6.3	4.8
irudayaraj	50	M	Y	DM	NIL	156	100	168	22	0.7	6.8	4.4	NSR	141	176	Rt MCA Infarc	60.2	7.57	1.51
Srinivasan	52	M	N	DM	NIL	120	80	156	35	0.8	6.4	4.6	NSR	126	185		79.9	6.07	3.56
Subrmaniam	80	M	Y	DM	S/A	160	102	182	25	0.9	6.7	4	NSR	108	218	Lt MCA Infarct	89.2	6.53	2.14
Ravi	78	M	N	DM	S/A	120	80	144	23	0.7	6.5	4.3	NSR	116	174		52.8	5.9	2.02
Rajarajan	50	M	Y	DM	S/A	168	100	146	33	0.8	6.9	4.1	NSR	128	146	Rt MCA Infarc	46.8	8.21	1.78
Vimal	52	M	N	DM	S/A	110	80	168	38	0.8	6.8	3.9	NSR	108	165		75.2	8.3	1.11
Kannan	60	M	Y	DM	S/A	150	100	138	31	0.7	6.4	4.4	NSR	142	214	Rt MCA Infarc	77.8	4.81	2.06
Basheer	62	M	N	DM	S/A	130	80	142	37	0.8	6.7	4.6	NSR	140	162		89.6	6.09	0.58
Sukumaran	62	M	Y	DM	S/A	160	100	134	27	0.7	6.5	4	NSR	162	190	Rt MCA Infarc	48.1	4.71	0.98
Rajamanicka	65	M	N	DM	S/A	136	84	128	32	0.8	6.9	4.3	NSR	160	189		64.9	5.79	1.98
Govindsamy	65	M	Y	HT	S/A	160	104	101	36	0.9	7.2	4.1	NSR	132	190	Rt MCA Infarc	70.2	7.66	1.68
Daniel	66	M	N	HT	S/A	150	90	88	32	0.7	6.8	4.5	NSR	130	172		72.3	6.3	1.86
Chandraseka	62	M	Y	HT	S/A	160	90	92	26	0.8	6.5	4.3	NSR	142	201	Rt MCA Infarc	42.7	4.62	1.79
Pichaikaran	65	M	N	HT	S/A	150	90	106	36	0.8	6.9	3.9	NSR	141	164		81.6	11.01	1.19
Arokiam	50	M	Y	HT	S/A	160	100	98	28	0.7	6.8	4.4	NSR	126	188	Rt MCA Infarc	70.3	5.8	1.04
Salim	53	M	N	HT	S/A	150	90	93	22	0.8	6.4	4.6	NSR	108	182		123.4	7.88	2.62
Ramu	60	M	Y	HT	S/A	170	100	103	35	0.7	6.7	4	NSR	116	180	Rt MCA Infarc	67.5	5.77	0.73
Senthil	62	M	N	HT	S/A	150	90	107	25	0.8	6.5	4.3	NSR	128	168		78.2	9.1	1.33
Mohanavelu	62	M	Y	HT	S/A	178	100	95	32	0.8	6.9	4.1	NSR	108	165	Lt MCA Infarct	64.3	9.38	0.55
Ganapathy	65	M	N	HT	NIL	160	90	101	36	0.9	7.2	4.5	NSR	142	177		82.1	5.86	1.27
Syed	65	M	Y	HT	NIL	170	100	98	32	0.7	6.8	4.3	NSR	140	180	Rt MCA Infarc	75.5	4.58	2.11
Munusamy	62	M	N	HT	NIL	160	96	102	26	0.7	7.2	4.3	NSR	162	165		68.5	7.41	1.85
Antony	71	M	Y	DM	NIL	164	100	156	36	0.9	6.8	3.9	NSR	160	162	Rt MCA Infarc	55.1	9.36	0.88
Pichai	70	M	N	DM	NIL	120	80	149	28	0.7	6.5	4.4	NSR	132	170		65.4	4.8	0.68
Rahim	74	M	Y	DM	NIL	166	102	127	32	0.8	6.9	4.6	NSR	130	198	Rt MCA Infarc	78.4	6.23	1.64
Govindaraj	70	M	N	DM	NIL	130	80	145	33	0.9	6.8	4	NSR	142	201		76.2	7.66	1.51
Abdul	72	M	Y	DM	NIL	160	100	158	32	0.7	6.4	4.3	NSR	141	178	Lt MCA Infarct	42.7	5.89	2.08
Eswaran	69	M	N	DM	NIL	110	80	132	36	0.9	6.7	4.1	NSR	126	184		68.3	7.26	1.56
Murugan	52	M	Y	DM	NIL	168	90	142	32	0.7	6.5	4.4	NSR	108	194	Rt MCA Infarc	69.9	5.41	1.34
Mohamad	55	M	N	DM	NIL	130	80	168	26	0.8	6.9	4.6	NSR	116	166		103.3	7.2	1.96
Gopal	62	M	Y	SHT/DM	NIL	180	98	172	28	0.7	6.8	4.5	NSR	106	180	Lt MCA Infarct	103.3	6.07	1.26

Srinivasan	65	M	N	SHT/DM	NIL	150	90	144	30	0.8	6.7	4.3	NSR	171	170		65.5	4.71	2.06
Ravi	70	M	Y	DM	S/A	190	100	168	28	0.8	6.8	4.6	NSR	126	170	Lt MCA Infarc	53.5	6.07	1.32
Ramasamy	72	M	N	DM	S/A	130	86	172	30	0.7	6.9	4.8	NSR	130	162		80.4	8.2	0.9
Sekar	60	M	Y	DM	S/A	160	100	147	31	0.7	6.4	4.4	NSR	142	178	Rt MCA Infarc	77.8	4.83	2.06
Perumal	62	M	N	DM	S/A	130	80	143	37	0.8	6.7	4.6	NSR	140	180		115.1	7.26	0.58
Soundarrajar	62	M	Y	DM	S/A	160	90	158	27	0.7	6.5	4	NSR	155	168	Rt MCA Infarc	65.8	4.06	0.98
Ponnusamy	65	M	N	DM	S/A	130	80	146	32	0.8	6.9	4.3	NSR	160	159		83.2	5.89	1.98
Vadivel	65	M	Y	HT	S/A	176	96	101	36	0.9	7.2	4.1	NSR	132	168	Rt MCA Infarc	81.9	6.67	1.68
Durai	66	M	N	HT	S/A	150	90	88	32	0.7	6.8	4.5	NSR	143	172		76.1	7.4	1.86
Kannan	62	M	Y	HT	S/A	160	100	92	26	0.8	6.5	4.3	NSR	142	178	Rt MCA Infarc	74	9.38	2.08
Maran	65	M	N	HT	S/A	150	90	106	36	0.8	6.9	3.9	NSR	141	164		87.2	5.86	2.64
Nagarajan	50	M	Y	HT	S/A	162	90	98	28	0.7	6.8	4.4	NSR	166	162	Rt MCA Infarc	57.7	6.54	2.84
Murugavel	53	M	N	HT	S/A	148	88	93	22	0.8	6.4	4.6	NSR	108	182		88.5	7.41	2.62
Ponnayan	60	M	Y	HT	S/A	170	96	103	35	0.7	6.7	4	NSR	116	141	Rt MCA Infarc	49.6	3.63	1.86
Dhandapani	62	M	N	HT	S/A	146	90	107	25	0.8	6.5	4.3	NSR	128	168		78.2	5.75	1.88
Sriram	62	M	Y	HT	NIL	140	100	95	32	0.8	6.9	4.1	NSR	108	170	Lt MCA Infarc	54.4	9.51	1.04
Bhasha	65	M	N	HT	NIL	150	90	101	36	0.9	7.2	4.5	NSR	142	182		67.8	5.46	2.02
Govindan	65	M	Y	HT	NIL	150	100	98	32	0.7	6.8	4.3	NSR	140	164	Rt MCA Infarc	53.9	4.89	2.11
Raman	62	M	N	HT	NIL	150	90	112	26	0.7	7.2	4.3	NSR	162	178		68.5	7.66	4.12
Gunaseelan	71	M	Y	DM	NIL	170	110	136	36	0.9	6.8	3.9	NSR	157	154	Rt MCA Infarc	72.3	5.89	0.88
Daniel	70	M	N	DM	NIL	110	80	128	28	0.7	6.5	4.4	NSR	132	160		65.4	6.02	0.68
Saleem	74	M	Y	DM	NIL	168	100	168	32	0.8	6.9	4.6	NSR	130	180	Rt MCA Infarc	59.8	4.21	1.64
Chandran	70	M	N	DM	NIL	130	80	180	33	0.9	6.8	4	NSR	142	201		76.2	9.1	1.63
Sivamurugar	75	M	Y	SHT	NIL	172	100	101	32	0.9	7.2	4.3	NSR	108	210	Rt MCA Infarc	80.8	6.56	7.05
Nagarajan	72	M	N	SHT	NIL	150	90	95	36	0.7	6.8	3.9	NSR	142	159		106.2	5.75	2.67
Sadasivam	57	M	Y	N	S/A	160	100	92	32	0.8	6.2	4.4	NSR	172	180	Lt MCA Infarc	87.7	6.34	2.04
Devan	58	M	N	N	S/A	110	80	96	36	0.8	6.8	4.6	NSR	162	172		78.2	6.3	0.8
Palani	75	M	Y	N	S/A	160	108	110	32	0.7	6.4	4	NSR	160	216	Rt MCA Infarc	65.5	5.79	7.56
Murugesan	72	M	N	N	S/A	120	70	100	26	0.8	6.7	4.3	NSR	132	164		74.4	6.67	0.92
Rajasekar	70	M	Y	N	S/A	160	100	101	36	0.8	6.5	4.1	NSR	126	188	Lt MCA Infarc	55.2	7.76	1.92
Natesan	71	M	N	N	S/A	120	80	94	28	0.9	6.9	4.4	NSR	142	146		58.4	61.5	1.86
Ramasamy	60	M	Y	N	NIL	164	100	98	32	0.7	6.8	4.6	NSR	141	176	Rt MCA Infarc	112.4	7.43	2.42
Palaniappan	62	M	N	N	NIL	120	80	89	33	0.7	6.4	4	NSR	123	168		88.9	8.13	2.46

Nagendran	70	M	Y	N	S/A	160	110	99	32	0.9	6.7	4.3	NSR	108	172	Rt MCA Infarc	71.4	8.48	1.42
Immanuel	71	M	N	N	S/A	130	80	102	36	0.7	6.5	4.1	NSR	116	158		76.5	7.5	1.48
Baskar	70	M	Y	N	NIL	156	100	101	32	0.8	6.9	4.5	NSR	128	201	Rt MCA Infarc	45.6	2.03	2.98
Kannappan	74	M	N	N	NIL	110	80	93	26	0.9	7.2	4.3	NSR	132	174		59.8	7.59	2.94
Sundar	70	M	Y	N	S/A	160	110	105	36	0.7	6.8	4.3	NSR	130	172	Lt MCA Infarc	62.2	7.13	3.46
Shanmugam	72	M	N	N	S/A	140	90	98	28	0.9	6.2	3.9	NSR	102	184		68.3	7.5	2.49
Thaiyabee	80	F	Y	N	NIL	160	106	98	36	0.7	7.2	4	NSR	128	156	Rt MCA Infarc	80.2	7.8	1.03
Kaniammal	76	F	N	N	NIL	140	90	102	28	0.8	6.8	4.3	NSR	132	174		90	5.75	2.02
Duraiammal	75	F	Y	N	NIL	172	108	99	22	0.8	7.2	4.1	NSR	130	190	Lt MCA Infarc	62.5	7.59	7.63
Pachaiamma	72	F	N	N	NIL	150	80	110	35	0.7	6.8	4.5	NSR	138	188		70.8	6.7	1.8
Kalaiarasi	56	F	Y	N	NIL	156	108	108	25	0.8	6.5	4.3	NSR	141	158	Rt MCA Infarc	55.2	6.53	1.79
Karthiayeni	58	F	N	N	NIL	120	70	94	23	0.7	6.9	4.3	NSR	126	148		78.4	4.83	1.03
Chokammal	80	F	Y	N	NIL	170	104	96	33	0.8	6.8	3.9	NSR	108	144	Rt MCA Infarc	84.3	5.9	1.19
Pushpa	78	F	N	N	NIL	130	90	99	38	0.8	6.4	4.4	NSR	106	159		65.8	7.43	1.85
Neelavathi	63	F	Y	N	NIL	160	100	101	31	0.9	6.7	4.6	NSR	162	190	Lt MCA Infarc	56.6	7.13	1.72
Saraswathi	60	F	N	N	NIL	130	80	108	37	0.7	6.5	4	NSR	160	172		67.7	4.2	1.6
Pavalakodi	67	F	Y	HT	NIL	160	104	98	22	0.7	6.9	4.3	NSR	132	166	Rt MCA Infarc	79.2	6.3	1.22
Rukmani	68	F	N	HT	NIL	156	88	102	35	0.9	7.2	4.1	NSR	129	164		42.7	5.35	0.89
Revathy	80	F	Y	HT	NIL	170	90	96	25	0.7	6.8	4.3	NSR	142	178	Rt MCA Infarc	88.8	7.7	1.11
Pushpa	78	F	N	HT	NIL	130	90	98	23	0.8	6.4	4.3	NSR	141	182		53.9	6.29	1.33
Valli	71	F	Y	DM	NIL	172	100	162	33	0.9	6.7	3.9	NSR	133	160	Rt MCA Infarc	109.7	8.48	0.44
Porkodi	68	F	N	DM	NIL	130	70	144	38	0.7	6.5	4.4	NSR	108	168		65.8	6.54	1.27
Fathima	70	F	Y	DM	NIL	160	108	138	31	0.9	6.9	4.6	NSR	116	157	Lt MCA Infarc	51.3	7.43	1.85
Sundari	67	F	N	DM	NIL	120	80	144	37	0.7	7.2	4	NSR	128	175		62.2	6.7	2.04
Lakshmi	70	F	Y	DM	NIL	168	100	136	27	0.7	6.8	4.3	NSR	132	180	Rt MCA Infarc	52.3	4.77	1.06
Poongavana	68	F	N	DM	NIL	130	84	140	32	0.8	6.7	4.1	NSR	130	162		55.1	5.51	1.43
Chinnaponnu	72	F	Y	DM/HT	NIL	170	100	130	36	0.8	6.5	4.3	NSR	142	168	Lt MCA Infarc	82.1	6.53	1.74
Vaduvambal	70	F	N	DM/HT	NIL	136	90	148	32	0.7	6.9	3.9	NSR	139	184		55.5	8.4	0.48
Saraswathi	74	F	Y	DM/HT	NIL	180	100	140	25	0.8	7.2	4.4	NSR	126	180	Rt MCA Infarc	109.4	8.3	0.57
Ponnamal	76	F	N	DM/HT	NIL	140	80	152	23	0.7	6.8	4.6	NSR	108	148		53.4	7.9	1.05
Roopavathy	72	F	Y	DM/HT	NIL	180	110	122	33	0.8	6.4	4	NSR	156	184	Rt MCA Infarc	59.6	8.5	1.38
Ayisha Begu	75	F	N	DM/HT	NIL	146	90	142	38	0.8	6.7	4.3	NSR	141	174		67.8	7.9	0.56
Lakshmi	65	F	Y	HT	NIL	170	90	98	31	0.9	6.5	4.1	NSR	126	220	Lt MCA Infarc	90	4.77	2.12

Thangamani	62	F	N	HT	NIL	140	90	93	37	0.7	6.9	4.3	NSR	108	165		65.5	7.59	2.62
Rukmani	73	F	Y	HT	NIL	180	110	102	22	0.7	7.2	4.3	NSR	154	208	Rt MCA Infarc	64.1	5.26	6.22
Jothi	71	F	N	HT	NIL	150	90	98	35	0.9	6.8	3.9	NSR	162	160		78.4	9.36	1.03
Kannama	66	F	Y	DM	NIL	160	100	126	25	0.7	6.7	4.4	NSR	160	174	Rt MCA Infarc	89.8	4.52	1.54
Bharathy	63	F	N	DM	NIL	150	90	142	25	0.8	6.5	4.6	NSR	132	159		55	5.51	1.43
Krishnaveni	58	F	Y	N	NIL	150	100	92	23	0.9	6.9	4	NSR	149	193	Rt MCA Infarc	48.6	6.53	1.74
Gandhimath	55	F	N	N	NIL	140	80	94	33	0.7	7.2	4.3	NSR	142	172		61	7.5	4.69
Padmini	72	F	Y	HT	NIL	170	90	101	38	0.9	6.8	4.1	NSR	141	211	Lt MCA Infarc	90	5.75	2.12
Saroja	67	F	N	HT	NIL	150	90	99	31	0.7	6.4	4.3	NSR	126	164		65.5	7.59	2.62
Visalakshi	65	F	Y	N	NIL	168	100	94	37	0.8	6.7	3.9	NSR	108	147	Rt MCA Infarc	84.3	5.9	1.28
Chellatha	62		N	N	NIL	130	70	97	27	0.8	6.5	4.4	NSR	162	205		64.1	5.26	2.12
Venmani	73	F	Y	N	NIL	180	110	103	32	0.7	6.9	4.6	NSR	128	158	Lt MCA Infarc	78.4	9.36	1.03
Valliammal	69	F	N	N	NIL	120	80	93	36	0.8	7.2	4	NSR	132	168		85.6	4.38	1.46
Saraswathi	72	F	Y	DM/HT	NIL	170	100	124	36	0.8	6.5	4.3	NSR	140	188	Rt MCA Infarc	140.5	7.13	1.72
Malliga	68	F	N	DM/HT	NIL	140	90	138	32	0.7	6.9	3.9	NSR	141	184		61.5	8.13	0.73
Fathimabeev	70	F	Y	DM/HT	NIL	160	106	140	25	0.8	7.2	4.4	NSR	138	196	Rt MCA Infarc	109.4	4.44	0.57
Parvathy	72	F	N	DM/HT	NIL	138	80	162	23	0.7	6.8	4.6	NSR	108	185		114.3	7.9	1.05
Soundari	62	F	Y	DM/HT	NIL	154	104	160	33	0.8	6.4	4	NSR	142	170	Rt MCA Infarc	59.6	8.5	1.38
Shanthi	65	F	N	DM/HT	NIL	140	80	128	38	0.8	6.7	4.3	NSR	138	198		46.8	4.91	5.49
Patchayamm	69	F	Y	HT	NIL	162	100	98	31	0.9	6.5	4.1	NSR	126	162	Lt MCA Infarc	88.8	4.52	1.11
Poorani	66	F	N	HT	NIL	140	90	93	37	0.7	6.9	4.3	NSR	108	165		100.3	5.01	0.62
Pavalam	72	F	Y	N	NIL	170	100	102	22	0.7	7.2	4.3	NSR	162	142	Rt MCA Infarc	59.9	5.26	1.43
Kanammal	70	F	N	N	NIL	120	86	98	35	0.9	6.8	3.9	NSR	154	160		78.4	6.6	1.08
Mythili	66	F	Y	DM	NIL	150	106	186	25	0.7	6.7	4.4	NSR	146	190	Rt MCA Infarc	62.4	6.9	1.03
Vaniyammal	63	F	N	DM	NIL	130	80	154	25	0.8	6.5	4.6	NSR	132	159		79.2	6.8	1.3
Lakshmi	58	F	Y	N	NIL	160	100	92	23	0.9	6.9	4	NSR	123	180	Rt MCA Infarc	78.4	9.36	1.04
Chinnathayi	60	F	N	N	NIL	120	70	94	33	0.7	7.2	4.3	NSR	142	164		85.7	6.7	2.04
Neelakodi	70	F	Y	HT	NIL	170	100	101	38	0.9	6.8	4.1	NSR	141	170	Lt MCA Infarc	39.4	7.43	1.85
Aftuz Begum	67	F	N	HT	NIL	15	90	99	31	0.7	6.4	4.3	NSR	116	148		84.3	5.9	1.19
Mariammal	65	F	Y	N	NIL	162	100	94	37	0.8	6.7	3.9	NSR	108	164	Rt MCA Infarc	74.8	7.8	1.29
Mary	62	F	N	N	NIL	130	80	97	27	0.8	6.5	4.4	NSR	167	182		61.5	6.5	1.44
Kalaivani	72	F	Y	N	NIL	168	102	103	32	0.7	6.9	4.6	NSR	128	190	Lt MCA Infarc	61.5	8.13	0.73
Valli	69	F	N	N	NIL	136	80	93	36	0.8	7.2	4	NSR	132	168		85.6	8.5	1.46

Fathima	72	F	Y	N	NIL	170	96	94	37	0.8	6.7	3.9	NSR	108	206	Rt MCA Infarc	74.8	7.8	6.76
Poongavana	69	F	N	N	NIL	130	70	97	27	0.8	6.5	4.4	NSR	156	182		61.5	6.5	1.03
Saroja	71	F	Y	N	NIL	160	90	103	32	0.7	6.9	4.6	NSR	128	164	Lt MCA Infarc	61.5	8.13	0.73
Kanniammal	70	F	N	N	NIL	120	80	93	36	0.8	7.2	4	NSR	165	168		85.6	8.5	1.46
Selvi	62	F	Y	DM	NIL	160	100	122	25	0.7	6.7	4.4	NSR	160	155	Rt MCA Infarc	62.4	6.9	1.03
Isabel	60	F	N	DM	NIL	140	80	158	25	0.8	6.5	4.6	NSR	132	159		49.6	5.08	2.49
Varadhamba	65	F	Y	N	NIL	164	100	92	23	0.9	6.9	4	NSR	133	180	Rt MCA Infarc	66.8	3.67	2.46
Shenbagam	67	F	N	N	NIL	120	70	94	33	0.7	7.2	4.3	NSR	145	172		84.3	5.8	1.19

INSTITUTIONAL ETHICAL COMMITTEE
GOVT.KILPAUK MEDICAL COLLEGE,
CHENNAI-10
Ref.No.3182/ME-1/Ethics/2014 Dt:08.05.2014.
CERTIFICATE OF APPROVAL

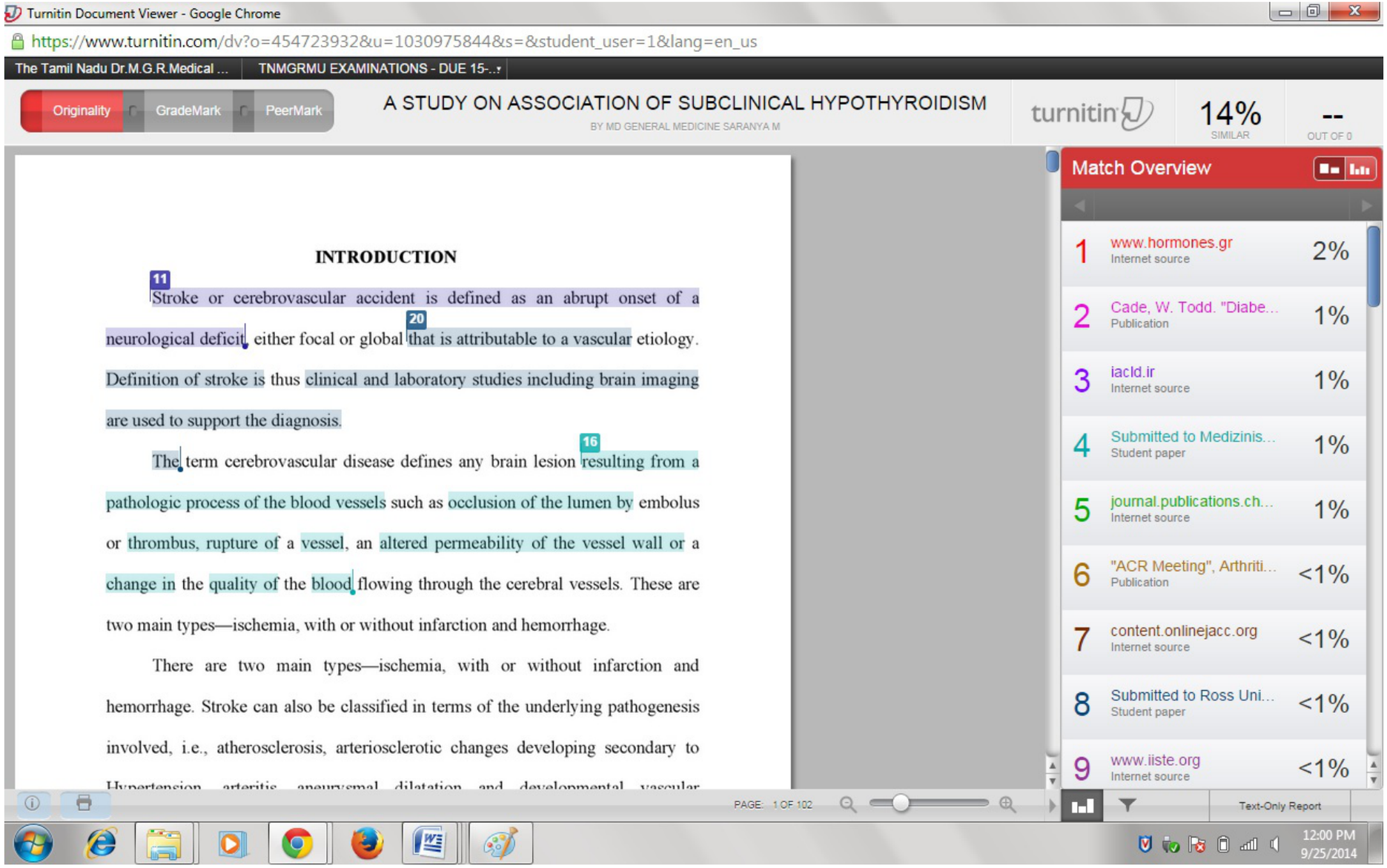
The Institutional Ethical Committee of Govt. Kilpauk Medical College, Chennai reviewed and discussed the application for approval "A Study on association of subclincal hypothyroidism with acute ischemic stroke" – For Project Work submitted by Dr.M.Saranya, MD (GM), PG Student, KMC, Chennai-10.

The Proposal is APPROVED.

The Institutional Ethical Committee expects to be informed about the progress of the study any Adverse Drug Reaction Occurring in the Course of the study any change in the protocol and patient information /informed consent and asks to be provided a copy of the final report.

GOVT. KILPAUK MEDICAL COLLEGE
30 MAY 2014
Kilpauk, Chennai-10.

CHAIRMAN, 30/5/14.
Ethical Committee
Govt.Kilpauk Medical College,Chennai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INTRODUCTION
11
Stroke or cerebrovascular accident is defined as an abrupt onset of a neurological deficit, either focal or global 20 that is attributable to a vascular etiology. Definition of stroke is thus clinical and laboratory studies including brain imaging are used to support the diagnosis.
The term cerebrovascular disease defines any brain lesion 16 resulting from a pathologic process of the blood vessels such as occlusion of the lumen by embolus or thrombus, rupture of a vessel, an altered permeability of the vessel wall or a change in the quality of the blood flowing through the cerebral vessels. These are two main types—ischemia, with or without infarction and hemorrhage.
There are two main types—ischemia, with or without infarction and hemorrhage. Stroke can also be classified in terms of the underlying pathogenesis involved, i.e., atherosclerosis, arteriosclerotic changes developing secondary to
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